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Zur Erklärung der Zweibuchstaben-Codes, und der anderen Abkürzungen wird auf die Erklärungen ("Guidance Notes on Codes and Abbreviations") am Anfang jeder regulären Ausgabe der PCT-Gazette verwiesen.

WO 01/16303 A2

(54) Title: NUCLEIC ACIDS WHICH CODE FOR THE ENZYME ACTIVITIES OF THE SPINOSYN BIOSYNTHESIS

(54) Bezeichnung: NUCLEINSÄUREN, DIE FÜR ENZYMAKTIVITÄTEN DER SPINOSYN-BIOSYNTHESE CODIEREN

(57) Abstract: The present invention relates to nucleic acids which code for the enzyme activities of the spinosyn biosynthesis. The invention also relates to the corresponding enzymes as such. The invention further relates to a method for producing spinosyn derivatives and spinosyn precursors.

(57) Zusammenfassung: Die vorliegende Erfindung betrifft Nucleinsäuren, die für Enzymaktivitäten der Spinosyn-Biosynthese codieren, sowie die entsprechenden Enzyme per se. Weiterhin betrifft die Erfindung Verfahren zum Herstellen von Spinosyn-Derivaten und -Vorstufen.

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Nucleinsäuren, die für Enzymaktivitäten der Spinosyn-Biosynthese codieren

Die vorliegende Erfindung betrifft Nucleinsäuren, die für Enzymaktivitäten der Spinosyn-Biosynthese codieren, sowie die entsprechenden Enzyme per se.

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Spinosyne stellen eine neue Gruppe von makrolidischen Verbindungen dar, die aus dem Actinomyceten *Saccharopolyspora spinosa* isoliert worden sind (Mertz und Yao, 1990). Sie werden zur Bekämpfung von Insekten eingesetzt (WO 97/00265, WO 94/20518, WO 93/09126, US 5670364, US 5362634, US 5227295, US 5202242). Spinosyne zeigen eine starke insektizide, jedoch keine antibakterielle Aktivität, wodurch sie von den konventionellen Makroliden, wie Tylosin, Spiramycin und Erythromycin, die keine insektizide, jedoch antimikrobielle Wirksamkeit aufweisen, unterscheidbar sind.

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Die Struktur der Spinosyne setzt sich zusammen aus einem tetracyclischen Polyketidgrundgerüst (Aglycon) mit einem 12-gliedrigen Makrolidring und einem 5,6,5-cis-anti-trans-Tricyclus, sowie einem D-Forosamin- und einem 2,3,4-Tri-O-Methyl-L-Rhamnose-Zuckeranteil (Kirst et al., 1991). Mehr als 20 verschiedene natürliche Spinosyn-Derivate, der sogenannte A83543 Komplex, ist bisher beschrieben worden (WO 97/00265, WO 94/20518, WO 93/09126). Diese Derivate variieren in der Substitution von einer oder einigen Methylgruppen am tetracyclischen Grundgerüst, am Forosamin- oder am Tri-Methyl-Rhamnose-Zuckeranteil. Ein 17-Pseudoaglycon, dem der Forosamin-Zuckeranteil fehlt, ist ebenfalls aus Kulturbrühen von *S. spinosa* isoliert worden.

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Die Hauptkomponenten des von *S. spinosa* gebildeten A83543 Komplexes stellen die Varianten Spinosyn A und Spinosyn D dar, die die wesentlichen Bestandteile des Produktes Spinosad darstellen (vgl. Pesticide Manual, British Crop Protection Council, 11th Ed., 1997, Seite 1272 und Dow Elanco trade magazine Down to Earth, Vol. 52, NO.: 1, 1997 und die darin zitierte Literatur).

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- Aufbauend auf Untersuchungen zum Einbau von C^{13} -markiertem Acetat, Propionat, Butyrat oder Isobutytrat konnte gezeigt werden, dass die Biosynthese von A83543 einem Polyketid-Biosyntheseweg folgt (Nakatsukasa et al., 1990). Polyketide werden durch multifunktionelle Enzyme, den sog. Polyketidsynthasen (PKS's) aus kurz-
- 5 kettigen Säurebausteinen wie Acetat, Propionat oder Butyrat aufgebaut. Ähnlich wie die verwandten Fettsäuresynthasen (FAS's) katalysieren sie decarboxylierende Polykondensationsschritte der als CoA-Thioester aktivierten Bausteine. Während FAS's nach jedem Kondensationsschritt eine vollständige Reduktion der intermediär an der wachsenden Polyketidkette entstehenden β -Oxoester durch Ketoreduktion, Dehy-
- 10 dratation und Enoylreduktion katalysieren, können PKS's bestimmte Reduktionsschritte auslassen. Modulare Typ I PKS's bestehen aus einem oder mehreren großen multifunktionalen Proteinen. Iterative Typ II PKS's stellen dagegen einen Komplex aus weitgehend monofunktionalen Proteinen dar.
- 15 Die enzymatischen Aktivitäten von modularen Typ I PKS's lassen sich zu sogenannten Modulen zusammenfassen. Hierbei trägt ein Modul eine Anordnung von drei enzymkatalytisch aktiven Domänen, die zu einer Verlängerung der wachsenden Polyketidkette um eine biosynthetische Verlängerungseinheit führen. Bei diesen Domänen handelt es sich um eine β -Ketoacyl:Acyl Carrier Protein Synthase-
- 20 Domäne, eine Acyltransferase-Domäne und eine β -Ketoacyl:Acyl Carrier Protein-Domäne. Ein Modul kann auch eine Ketoreduktase-, eine Dehydratase-, eine Enoylreduktase- und eine Thioesterase-Domäne tragen. Ein sog. Ladungsmodul, das am Beginn der Biosynthese steht kann von den genannten Domänen lediglich eine Acyltransferase-Domäne und eine β -Ketoacyl:Acyl-Carrier Protein-Domäne tragen, sowie
- 25 eine enzymatisch inaktive β -Ketoacyl:Acyl Carrier Protein Synthase-Domäne. Eine Polyketidsynthase-Domäne umfasst jeweils eine dieser genannten enzymatischen Aktivitäten.
- 30 Aufgrund der potenten insektiziden Wirkung sowie der bemerkenswerten Struktur der Spinosyne besteht ein großes Interesse, die genetischen Informationen für deren Biosynthese zu entschlüsseln.

Gegenstand der Erfindung sind Nucleinsäuren, welche zumindest eine Region umfassen, die für eine Enzymaktivität codiert, welche an der Biosynthese von Spinosynen beteiligt ist.

5

Die vorliegende Erfindung stellt ein Cluster von offenen Leserahmen (ORF's) bereit, deren Translationsprodukte an der Biosynthese von Spinosynen beteiligt sind. Weiterhin werden zusätzliche Gene bzw. ORF's bereitgestellt, die außerhalb des ca. 120 kb großen Spinosyn-Biosynthesecusters liegen, und deren Translationsprodukte an der Rhamnose-Zuckerbiosynthese beteiligt sind.

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Bei den erfindungsgemäßen Nucleinsäuren handelt es sich insbesondere um einzelsträngige oder doppelsträngige Desoxyribonucleinsäuren (DNA) oder Ribonucleinsäuren (RNA). Bevorzugte Ausführungsformen sind Fragmente genomischer DNA und cDNA's.

15

Der Ausdruck "zumindest eine Region", wie er hierin verwendet wird, bedeutet, dass die erfindungsgemäße Nucleinsäure eine oder mehrere Sequenzen umfassen kann, welche jeweils für einzelne Aktivitäten codieren, die Schritte bei der Synthese von Spinosynen durchführen. Es werden demnach auch Nucleinsäuren als erfindungsgemäß betrachtet, die nur für eine einzige Enzymaktivität der Spinosyn-Biosynthese codieren.

20

Der Ausdruck "Enzymaktivität", wie er hierin verwendet wird, bedeutet, dass ausgehend von den hierin betrachteten Nucleinsäuren zumindest derjenige Teil eines vollständigen Enzyms exprimiert werden kann, der noch die Katalyseeigenschaften des Enzyms ausübt.

25

Insbesondere codieren die erfindungsgemäßen Nucleinsäuren für Enzymaktivitäten von Polyketidsynthasen, Methyltransferasen, Epimerasen, Glycosyltransferasen,

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Aminotransferasen, Dimethyltransferasen, Reduktasen, Dehydratasen und/oder Cyclisierungsenzymen.

5 Bevorzugt handelt es sich bei den erfindungsgemäßen Nucleinsäuren um DNA-Fragmente, die genomischer DNA von *S. spinosa* entsprechen.

Besonders bevorzugt umfassen die erfindungsgemäßen Nucleinsäuren zumindest eine Sequenz ausgewählt aus

- 10 (a) den Sequenzen gemäß SEQ ID NOS: 1, 2, 3, 4, 5, 7, 9, 11, 13, 15, 17, 19, 21, 23, 25, 27, 29, 31, 33, 35, 37, 39, 41, 43, 45, 47, 49, 51, 52 oder 54,
 - 15 (b) zumindest 14 Basenpaare langen Teilsequenzen der unter (a) definierten Sequenzen,
 - (c) Sequenzen, welche an die unter (a) definierten Sequenzen hybridisieren,
 - 20 (d) Sequenzen, welche eine zumindest 70 %ige, bevorzugt eine 80 %ige, besonders bevorzugt eine 90 %ige Identität zu den unter (a) definierten Sequenzen aufweisen,
 - 25 (e) Sequenzen, welche zu den unter (a) definierten Sequenzen komplementär sind, und
 - (f) Sequenzen, welche aufgrund der Degeneriertheit des genetischen Codes für dieselbe Aminosäuresequenz kodieren wie die unter (a) bis (d) definierten Sequenzen.
- 30

Der Ausdruck "hybridisieren", wie er hierin verwendet wird, beschreibt den Vorgang, bei welchem ein einzelsträngiges Nucleinsäuremolekül mit einem komplementären Strang eine Basenpaarung eingeht. Auf diese Weise können beispielsweise ausgehend von genomischer DNA aus Organismen, die phylogenetisch mit *S. spinosa* verwandt sind und die Fähigkeit der Biosynthese von Spinosynen besitzen, DNA-Fragmente isoliert werden, welche dieselben Eigenschaften wie die aus *S. spinosa* isolierten Fragmente aufweisen.

Bevorzugte Hybridisierungsbedingungen sind nachstehend angegeben: Hybridisierungslösung: 5 x SSC; Blocking Reagents (Roche Diagnostics GmbH, Mannheim, Deutschland), 1 %; N-Lauroylsarcosin, 0,1 %; SDS (Sodiumdodecylsulfate) 0,02 %; Hybridisierungstemperatur: 60°C; erster Waschschrift: 2 x SSC bei 60°C; zweiter Waschschrift: 2 x SSC bei 60°C; bevorzugt zweiter Waschschrift: 0,5 x SSC bei 60°C; besonders bevorzugt zweiter Waschschrift: 0,2 x SSC bei 60°C.

Der Grad der Identität der Nucleinsäuren wird vorzugsweise bestimmt mit Hilfe des Programms GAP aus dem Programmpaket GCG (Devereux et al., 1984), Version 9.1 unter Standardeinstellungen.

Besonders hervorgehoben werden Nucleinsäuren, die

- (1) entweder alle Sequenzen, die für Schritte der Forosamin- und Trimethyl-Rhamnose-Biosynthese codieren, umfassen, insbesondere die Sequenzen gemäß SEQ ID NOS: 4 und 51, oder
- (2) alle Sequenzen, die für Schritte der Polyketidsynthese codieren, umfassen, insbesondere die Sequenzen gemäß SEQ ID NOS: 5 und 6, oder
- (3) alle Sequenzen, die für alle Schritte der Forosamin-, Trimethyl-Rhamnose- und Polyketidsynthese codieren, umfassen, insbesondere die Sequenzen gemäß SEQ ID NOS: 1, 2, 3 und 51.

Alle zur Spinosyn-Biosynthese oder zur Synthese von Vorstufen, wie sie nachstehend definiert sind, benötigten DNA-Sequenzen können sich somit auf einem einzelnen Vektor befinden. Diese Nucleinsäuren können aber auch auf zwei oder mehreren Vektoren vorliegen und gleichzeitig oder nacheinander in einer Wirtszelle exprimiert werden.

Alle ORF's der erfindungsgemäßen Nucleinsäuren können von ihren eigenen Promotoren oder von heterologen Promotoren angeschaltet werden.

Gegenstand der vorliegenden Erfindung sind auch die regulatorischen Regionen, welche natürlicherweise, d.h. im Ursprungsorganismus *S. spinosa*, die Transkription der erfindungsgemäßen Nucleinsäuren kontrollieren.

Der Ausdruck "regulatorische Regionen", wie er hierin verwendet wird, bezieht sich auf Promotoren, Repressor- oder Aktivator-Bindungsstellen, Repressor- oder Aktivatorsequenzen, und Terminatoren. Ferner sind genetisch mobile Elemente, welche natürlicherweise, d.h. im Ursprungsorganismus *S. spinosa* vorkommen, ebenfalls von diesem Ausdruck umfasst. Solche genetisch mobilen Elemente können transposable oder mobilisierbare Elemente oder funktionelle Teile davon, IS-Elemente oder andere Insertionselemente sein. Weiterhin sind auch amplifizierbare DNA-Elemente (Amplifiable Units of DNA, AUD; Fishman and Hershberger, 1983), welche natürlicherweise, d.h. im Ursprungsorganismus *S. spinosa* vorkommen, von diesem Ausdruck umfasst. Die Erfindung betrifft auch jede Kombination dieser regulatorischen Regionen untereinander oder mit heterologen DNA-Fragmenten, wie z.B. Promotoren, Repressor oder Aktivator-Bindungsstellen, transposablen, mobilisierbaren oder transduzierbaren Elementen.

Gegenstand der vorliegenden Erfindung sind weiterhin DNA-Konstrukte, die zumindest eine erfindungsgemäße Nucleinsäure und einen heterologen Promotor umfassen.

Der Ausdruck "heterologer Promotor", wie er hierin verwendet wird, bezieht sich auf einen Promotor, der im Ursprungsorganismus nicht die Expression des betreffenden Gens (ORF's) kontrolliert.

5 Die Auswahl von heterologen Promotoren ist davon abhängig, ob zur Expression pro- oder eukaryotische Zellen oder zellfreie Systeme verwendet werden. Ein bevorzugtes Beispiele für einen heterologen Promotor ist der Promotor des *mel*-Gens aus dem Vektor pIJ702 (The John Innes Foundation, Norwich, UK 1985). Die heterologe Expression kann z.B. eingesetzt werden, um zu einer Steigerung der Produktion von
10 Spinosyn im Vergleich zum natürlichen Spinosyn-Produzenten zu gelangen.

Gegenstand der Erfindung sind ferner Vektoren, die zumindest eine der erfindungsgemäßen Nucleinsäuren enthalten. Als Vektoren können alle in molekularbiologischen Laboratorien verwendeten Phagen, Plasmide, Phagmide, Phasmide,
15 Cosmide, YACs, BACs, PACs, künstliche Chromosomen oder Partikel, die für einen Partikelbeschuss geeignet sind, verwendet werden.

Bevorzugt sind BAC-Vektoren. BAC-Vektoren (Bacterial Artificial Chromosome) sind entwickelt worden zur Klonierung von großen DNA-Fragmenten (Shizuya et al.,
20 1992). Es handelt sich um "single-copy" Plasmide mit einem F-Faktor Origin, die DNA-Fragmente mit einer durchschnittlichen Größe von 120 Kilobasenpaaren (kb) tragen können. Sie sind replizierbar in *Escherichia coli*. Der BAC-Vektor pBeloBAC11 (Kim et al., 1996) trägt einen T7 und einen SP6 Promotor, welche die Klonierungsstelle flankieren und als Startbereich für Sequenzierungsprimer sowie
25 zur Generierung von RNA-Transkripten verwendet werden können.

Besonders bevorzugt sind die am 18. August 1999 bei der Deutschen Sammlung von Mikroorganismen und Zellkulturen GmbH (DSMZ), Mascheroder Weg 1b, D-38124 Braunschweig, in Übereinstimmung mit den Bestimmungen des Budapester Ver-
30 trages unter den Hinterlegungsnummern DSM 13010, DSM 13011 und DSM 13012 hinterlegten BAC-Shuttleklone, die Gegenstand der vorliegenden Erfindung sind.

Die hinterlegten BAC-Shuttleklone P11/G6, P8/G11 und P11/B10 tragen jeweils ein mindestens 100 kb großes DNA-Fragment aus *S. spinosa*. Die Klone P11/G6 und P11/B10 tragen jeweils einen Teil der Nucleinsäuresequenz gemäß SEQ ID NO: 4, sowie die angrenzenden vollständigen Nucleinsäuresequenzen gemäß SEQ ID NOS: 5 und 6, sowie einen an die Nucleotidsequenz gemäß SEQ ID NO: 6 3'-angrenzende DNA-Bereich (Abb. 7). Der Klon P8/G11 trägt einen Teil der Nucleinsäuresequenz gemäß SEQ ID NO: 6, die vollständigen Nucleinsäuresequenzen gemäß SEQ ID NOS: 5 und 4, sowie einen an die Sequenz gemäß SEQ ID NO: 4 3'-angrenzenden DNA-Bereich (Abb. 7).

In gleicher Weise sind auch PAC- und alle anderen funktionell gleichwertigen Vektoren, die es erlauben, große DNA-Fragmente, insbesondere solche DNA-Fragmente, die größer als 30 kb, vorzugsweise größer als 40 kb, besonders bevorzugt größer als 60 kb sind, in heterologe Wirtszellen zu übertragen und dort eine Etablierung von Fremd-DNA zu gewährleisten, für eine Spinosyn-Produktion geeignet. Vorzugsweise werden solche BAC-, PAC- und funktionell gleichwertigen Vektoren verwendet, die zu einem Shuttle-Vektor modifiziert sind und z.B. eine Plasmidreplikation sowohl in Gram-negativen Bakterien, wie *Escherichia coli*, als auch in Gram-positiven Bakterien, wie *Streptomyces*, erlauben. Solche bevorzugten Shuttle-Vektoren können DNA-Fragmente einer Größe tragen, die in üblichen Vektoren, wie z.B. Cosmidvektoren, nicht klonierbar sind und nicht in heterologe Wirte, wie Actinomyceten, z.B. Streptomyceten, übertragbar sind. Letztere Vektoren können sowohl durch Transformation, Konjugation, Elektroporation, Protoplastentransformation oder andere geeignete Verfahren übertragen werden. In hervorragender Weise sind solche Shuttle-Vektoren innerhalb einer heterologen Population Gram-negativer oder Gram-positiver Bakterien, zwischen Gram-positiven und Gram-negativen Bakterien, zwischen Bakterien und Archaea, zwischen Pro- und Eukaryonten konjugativ übertragbar. Die in heterologe Wirte, wie z.B. Streptomyceten, übertragenen BAC-, PAC- oder funktionell gleichwertigen Shuttle-Vektoren können autonom repliziert werden oder ins Genom des Wirtes integriert

werden. Letztere Integration kann über homologe Rekombination, über einen Φ C31-Integrationsmechanismus (Hopwood et al., 1985), über ortsspezifische Integration, die von pSAM2 (Smokvina et al., 1990; WO 95/16046) determinierten Funktionen abhängt oder über Mini-Circle vermittelte Funktionen (Motamedi et al., 1995; WO 96/00282) erfolgen.

Solche Shuttle-Vektoren erlauben es, spezifische, durch außerordentlich große DNA-Bereiche determinierte Biosynthesewege von Primär- oder Sekundärmetaboliten, durch Transfer eines einzigen rekombinanten Vektors heterolog in besonders geeigneten Wirtszellen zu exprimieren. So kann das identifizierte Cluster für die Biosynthese von Spinosyn in Organismen, wie Actinomyceten, z.B. *Streptomyces*, durch Transfer eines einzigen rekombinanten Shuttle-Vektors ausgeprägt werden. Aufgrund der Größe dieses Biosyntheseclusters ist diese heterologe Expression der Spinosyn-Biosynthese mit einem einzigen Cosmidvektor nicht möglich. Die Übertragung eines rekombinanten BAC-, PAC- oder funktionell gleichwertigen Shuttle-Vektors, der die erfindungsgemäßen Nucleinsäuren trägt, kann zu einer signifikanten Steigerung der Produktion von Spinosyn im Vergleich zur Spinosyn-Produktion des Stammes *S. spinosa* oder abgeleiteter Mutanten mit erhöhter Spinosyn-Bildung führen. Zudem kann ein solcher, für die Spinosyn-Biosynthese codierender Shuttle-Vektor genutzt werden, um nach Übertragung in heterologe Wirtszellen deren Biosynthese- und Modifizierungsleistung auszunutzen, um zu einer signifikanten Modifizierung von Spinosyn oder Spinosyn-Biosynthesevorstufen zu gelangen. Hierdurch ist es zudem möglich, neue Spinosyn-Derivate durch den Transfer eines einzigen rekombinanten Vektors in heterologe Wirtszellen herzustellen.

Weiterhin können solche Shuttle-Vektoren verwendet werden, klonierte Biosynthesewege von Sekundärmetaboliten als Bestandteil eines einzigen rekombinanten Shuttle-Vektors genetisch zu modifizieren. Solche Modifizierungen können z.B. in einem *E. coli* Wirt durchgeführt werden, z.B. unter Ausnutzung von Rekombinationsereignissen unter Beteiligung des recA-Genproduktes oder der recE- und recT-Genprodukte (Muyrers et al., 1999). Weiterhin können solche Vektoren

durch *in vitro*-Verfahren, wie z.B. das Template Generation System (Finnzymes, FIN-02201, Espoo, Finnland) oder das Transposomics-System (Epicentre Technologies, Biozym Diagnostika GmbH, Oldendorf, Deutschland) modifiziert werden. Solche, für veränderte Biosynthesewege codierende Shuttle-Vektoren
5 können dann in geeignete Wirtszellen übertragen werden, um zur Produktion veränderter Sekundärmetabolite zu gelangen. In analoger Weise können die genannten Shuttle-Vektoren genutzt werden, die erfindungsgemäßen Nucleinsäuren zu modifizieren, um sie dann, nach Transfer in geeignete Wirtszellen zur Produktion veränderter Spinosyne einzusetzen.

10 Teile der erfindungsgemäßen Nucleinsäuren können auch als Bestandteil von zwei oder mehreren Vektoren, wie z.B. Cosmidvektoren, eine genetische Information determinieren, die in Kombination miteinander zur Biosynthese von Spinosyn oder Spinosyn-Vorstufen, wie z.B. Pseudoaglycon oder Spinosyn-Aglycon geeignet sind.
15 Solche Kombinationen von rekombinanten Vektoren können eingesetzt werden, um zu einer Spinosyn-Produktion in anderen Organismen als *S. spinosa* zu gelangen. Dies kann bei einer Expression in besonders geeigneten Wirten zu einer signifikanten Steigerung der Spinosyn-Produktion im Vergleich zu *S. spinosa* oder abgeleiteten produktionsverstärkten Mutanten führen. Weiterhin ist es möglich, erfindungsgemäße Nucleinsäuren in einzelnen rekombinanten Vektoren dieser Vektorkombination
20 so zu verändern, dass eine heterologe Produktion von Spinosyn-Derivaten in Wirtszellen möglich ist. Desweiteren kann eine solche Kombination von rekombinanten Vektoren durch deren Transfer in heterologe Wirte zur Bildung neuer Spinosyn-Derivate unter Ausnutzung des wirtseigenen Enzymsystems geeignet sein.

25 Gegenstand der vorliegenden Erfindung sind auch Wirtszellen, die zumindest eine der erfindungsgemäßen Nucleinsäuren enthalten. Als Wirtszelle eignen sich sowohl prokaryotische Zellen, vorzugsweise Actinomyceten, besonders bevorzugt Streptomyceten, als auch eukaryotische Zellen, wie Säugerzellen, Pflanzenzellen oder Hefezellen.
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In besonderer Weise können die erfindungsgemäßen Nucleinsäuren in pflanzliche Zellen übertragen und exprimiert werden. Hierdurch können transgene Pflanzen hergestellt werden, die das pflanzenschützende, insektizide Spinosyn bzw. Derivate davon produzieren. Eine Übertragung der erfindungsgemäßen Nucleinsäuren in die Pflanzenzellen oder pflanzliche Zellkulturen kann mit üblichen Verfahren u.a. auch durch Partikelbeschuss erfolgen.

Gegenstand der vorliegenden Erfindung sind weiterhin die Polypeptide, die von den erfindungsgemäßen Nucleinsäuren codiert werden. Die erfindungsgemäßen Polypeptide können ein vollständiges Enzym darstellen, das einen Schritt der Spinosyn-Biosynthese katalysiert. Jedoch sind auch solche Polypeptide von der Erfindung erfasst, die nur einen Teil der vollständigen Aminosäuresequenz des betreffenden Enzyms aufweisen.

Der Ausdruck "Teilsequenz", wie er hierin verwendet wird, bezieht sich somit auf die Aminosäuresequenz eines Polypeptids, das noch die Aktivität des entsprechenden vollständigen Enzyms oder einer enzymatisch aktiven Domäne ausüben kann.

Im Folgenden werden bevorzugte erfindungsgemäße Nucleinsäuren und Polypeptide mit Bezug auf die entsprechenden SEQ ID NOS näher charakterisiert.

SEQ ID NOS: 7 und 8, ORF1:

Nucleotidposition 828 bis 1 der SEQ ID NO: 4, 275 Aminosäuren;
das ableitbare Genprodukt ist eine Methyltransferase.

SEQ ID NOS: 9 und 10, ORF2:

Nucleotidposition 1.283 bis 2.455 der SEQ ID NO: 4, 390 Aminosäuren;
das ableitbare Genprodukt ist eine Glycosyltransferase.

SEQ ID NOS: 11 und 12, ORF3:

Nucleotidposition 2.495 bis 3.247 der SEQ ID NO: 4, 250 Aminosäuren;
das ableitbare Genprodukt ist eine Methyltransferase.

5 SEQ ID NOS: 13 und 14, ORF4:

Nucleotidposition 4.440 bis 3.253 der SEQ ID NO: 4, 395 Aminosäuren;
das ableitbare Genprodukt ist eine Methyltransferase.

SEQ ID NOS: 15 und 16, ORF5:

10 Nucleotidposition 4.578 bis 6.197 der SEQ ID NO: 4, 539 Aminosäuren;
das ableitbare Genprodukt ist ein C-C verknüpfendes Enzym, das Cyclisierungs-
reaktionen durchführt.

SEQ ID NOS: 17 und 18, ORF6:

15 Nucleotidposition 6.211 bis 7.404 der SEQ ID NO: 4, 397 Aminosäuren;
das ableitbare Genprodukt ist eine Methyltransferase.

SEQ ID NOS: 19 und 20, ORF7:

20 Nucleotidposition 7.401 bis 8.300 der SEQ ID NO: 4, 299 Aminosäuren;
das ableitbare Genprodukt ist eine Methyltransferase.

SEQ ID NOS: 21 und 22, ORF8:

25 Nucleotidposition 8.300 bis 9.466 der SEQ ID NO: 4, 388 Aminosäuren;
das ableitbare Genprodukt ist ein Enzym, das an Cyclisierungsreaktionen beteiligt ist.

SEQ ID NOS: 23 und 24, ORF9:

Nucleotidposition 10.572 bis 9.562 der SEQ ID NO: 4, 336 Aminosäuren.
das ableitbare Genprodukt ist eine 2,3-Reduktase.

SEQ ID NOS: 25 und 26, ORF10:

Nucleotidposition 12.029 bis 10.569 der SEQ ID NO: 4, 486 Aminosäuren;
das ableitbare Genprodukt ist eine 2,3-Dehydratase.

5 SEQ ID NOS: 27 und 28, ORF11:

Nucleotidposition 12.549 bis 12.109 der SEQ ID NO: 4, 146 Aminosäuren; das
ableitbare Genprodukt hat Homologien zu einer Thioesterase.

SEQ ID NOS: 29 und 30, ORF12:

10 Nucleotidposition 13.865 bis 12.546 der SEQ ID NO: 4, 439 Aminosäuren;
das ableitbare Genprodukt ist eine Glykosyltransferase.

SEQ ID NOS: 31 und 32, ORF13:

15 Nucleotidposition 14.245 bis 15.633 der SEQ ID NO: 4, 462 Aminosäuren;
das ableitbare Genprodukt ist eine 3,4-Dehydratase.

SEQ ID NOS: 33 und 34, ORF14:

20 Nucleotidposition 15.671 bis 16828 der SEQ ID NO: 4, 385 Aminosäuren;
das ableitbare Genprodukt ist eine 4-Aminotransferase.

SEQ ID NO: 35 und 36, ORF15:

Nucleotidposition 16.831 bis 17.580 der SEQ ID NO: 4, 249 Aminosäuren;
das ableitbare Genprodukt ist eine N-Dimethyltransferase.

25 SEQ ID NOS: 37 und 38, ORF16:

Nucleotidposition 18.930 bis 18.205 der SEQ ID NO: 4, 241 Aminosäuren;
das ableitbare Genprodukt ist eine 3,4-Reduktase.

SEQ ID NOS: 39 und 40, ORF17:

30 Nucleotidposition 19.025-19.861 der SEQ ID NO: 4, 278 Aminosäuren;
das ableitbare Genprodukt ist ein Transkriptions-Regulator.

SEQ ID NOS: 41 und 42, ORF18:

Nucleotidpositionen 116-7903 der SEQ ID NO: 5, Aminosäurepositionen 1 bis 2595:

- 5 Nucleotidpositionen 128-1402, Aminosäure Positionen 5-429 codieren eine β -Ketoacyl:Acyl Carrier Protein Synthase-Domäne;
- Nucleotidpositionen 1691-2656, Aminosäurepositionen 526-847 codieren eine Acyltransferase-Domäne;
- 10 Nucleotidpositionen 2798-3052, Aminosäurepositionen 895-979 codieren eine β -Ketoacyl:Acyl Carrier Protein-Domäne;
- Nucleotidpositionen 3107-4372, Aminosäurepositionen 998-1419 codieren eine β -Ketoacyl:Acyl Carrier Protein Synthase-Domäne;
- Nucleotidpositionen 4688-5662, Aminosäurepositionen 1525-1849 codieren eine Acyltransferase-Domäne;
- 15 Nucleotidpositionen 6587-7138, Aminosäurepositionen 2158-2341 codieren eine Ketoreduktase-Domäne;
- Nucleotidpositionen 7409-7666, Aminosäurepositionen 2432-2517 codieren eine β -Ketoacyl:Acyl Carrier Protein-Domäne.

20 SEQ ID NOS: 43 und 44, ORF19:

Nucleotidpositionen 7921-14379 der SEQ ID NO: 5, Aminosäurepositionen 1 bis 2152:

- Nucleotidpositionen 8029-9318, Aminosäurepositionen 37-466 codieren eine β -Ketoacyl:Acyl Carrier Protein Synthase-Domäne;
- 25 Nucleotidpositionen 9634-10608, Aminosäurepositionen 572-896 codieren eine Acyltransferase-Domäne;
- Nucleotidpositionen 10705-11259, Aminosäurepositionen 929-1113 codieren eine Dehydratase-Domäne;
- 30 Nucleotidpositionen 12043-13080, Aminosäurepositionen 1375-1720 codieren eine Enoylreduktase-Domäne;

Nucleotidpositionen 13093-13635, Aminosäurepositionen 1725-1905 codieren eine Ketoreduktase-Domäne;

Nucleotidpositionen 13885-14142, Aminosäurepositionen 1989-2074 codieren eine β -Ketoacyl:Acyl Carrier Protein-Domäne.

5

SEQ ID NOS: 45 und 46, ORF20:

Nucleotidpositionen 14424-23936 der SEQ ID NO: 5, Aminosäurepositionen 1 bis 3170:

10 Nucleotidpositionen 14523-15824, Aminosäurepositionen 34-467 codieren eine β -Ketoacyl:Acyl Carrier Protein Synthase-Domäne;

Nucleotidpositionen 16110-17075, Aminosäurepositionen 563-884 codieren eine Acyltransferase-Domäne;

Nucleotidpositionen 17997-18536, Aminosäurepositionen 1192-1371 codieren eine Ketoreduktase-Domäne;

15 Nucleotidpositionen 18795-19052, Aminosäurepositionen 1458-1543 codieren eine β -Ketoacyl:Acyl Carrier Protein-Domäne;

Nucleotidpositionen 19107-20387, Aminosäurepositionen 1562-1988 codieren eine β -Ketoacyl:Acyl Carrier Protein Synthase-Domäne;

20 Nucleotidpositionen 20718-21692, Aminosäurepositionen 2099-2423 codieren eine Acyltransferase-Domäne;

Nucleotidpositionen 22620-23171, Aminosäurepositionen 2733-2916 codieren eine Ketoreduktase-Domäne;

Nucleotidpositionen 23436-23693, Aminosäurepositionen 3005-3090 codieren eine β -Ketoacyl:Acyl Carrier Protein-Domäne.

25

SEQ ID NOS: 47 und 48, ORF21:

Nucleotidpositionen 23983-38757 der SEQ ID NO: 5, Aminosäurepositionen 1 bis 4924:

30 Nucleotidpositionen 24082-25392, Aminosäurepositionen 34-470 codieren eine β -Ketoacyl:Acyl Carrier Protein Synthase-Domäne;

- Nucleotidpositionen 25696-26661, Aminosäurepositionen 572-893 codieren eine Acyltransferase-Domäne;
- Nucleotidpositionen 26761-27315, Aminosäurepositionen 927-1111 codieren eine Dehydratase-Domäne;
- 5 Nucleotidpositionen 28231-28782, Aminosäurepositionen 1417-1600 codieren eine Ketoreduktase-Domäne;
- Nucleotidpositionen 29035-29265, Aminosäurepositionen 1685-1761 codieren eine β -Ketoacyl:Acyl Carrier Protein-Domäne;
- Nucleotidpositionen 29329-30624, Aminosäurepositionen 1783-2214 codieren eine β -Ketoacyl:Acyl Carrier Protein Synthase-Domäne;
- 10 Nucleotidpositionen 30928-31902, Aminosäurepositionen 2316-2640 codieren eine Acyltransferase-Domäne;
- Nucleotidpositionen 32827-33378, Aminosäurepositionen 2949-3132 codieren eine Ketoreduktase-Domäne;
- 15 Nucleotidpositionen 33652-33900, Aminosäurepositionen 3224-3306 codieren eine β -Ketoacyl:Acyl Carrier Protein-Domäne;
- Nucleotidpositionen 33952-35262, Aminosäurepositionen 3324-3760 codieren eine β -Ketoacyl:Acyl Carrier Protein Synthase-Domäne;
- Nucleotidpositionen 35554-36522, Aminosäurepositionen 3858-4180 codieren eine Acyltransferase-Domäne;
- 20 Nucleotidpositionen 37453-37998, Aminosäurepositionen 4491-4672 codieren eine Ketoreduktase-Domäne;
- Nucleotidpositionen 38254-38511, Aminosäurepositionen 4758-4843 codieren eine β -Ketoacyl:Acyl Carrier Protein-Domäne.
- 25
- SEQ ID NOS: 49 und 50, ORF22:
- Nucleotidpositionen 38808-50000 der SEQ ID NO: 5 und die Nukleotidpositionen 1 bis 5574 der SEQ ID NO: 6, Aminosäurepositionen 1 bis 5588:
- Nucleotidpositionen 38907-40226 der SEQ ID NO: 5, Aminosäurepositionen 34-473
- 30 codiert eine β -Ketoacyl:Acyl Carrier Protein Synthase-Domäne;

- Nucleotidpositionen 40494-41453 der SEQ ID NO: 5, Aminosäurepositionen 563-882 codieren eine Acyltransferase-Domäne;
- Nucleotidpositionen 41556-42119 der SEQ ID NO: 5, Aminosäurepositionen 917-1104 codieren eine Dehydratase-Domäne;
- 5 Nucleotidpositionen 43017-43568 der SEQ ID NO: 5, Aminosäurepositionen 1404-1587 codieren eine Ketoreduktase-Domäne;
- Nucleotidpositionen 43833-44090 der SEQ ID NO: 5, Aminosäurepositionen 1676-1761 codieren eine β -Ketoacyl:Acyl-Carrier Protein Domäne;
- Nucleotidpositionen 44151-45473 der SEQ ID NO: 5, Aminosäurepositionen 1782-2222 codieren eine β -Ketoacyl:Acyl Carrier Protein Synthase-Domäne;
- 10 Nucleotidpositionen 45765-46730 der SEQ ID NO: 5, Aminosäurepositionen 2320-2641 codieren eine Acyltransferase-Domäne;
- Nucleotidpositionen 46827-47459 der SEQ ID NO: 5, Aminosäurepositionen 2674-2884 codieren eine Dehydratase-Domäne;
- 15 Nucleotidpositionen 48378-48935 der SEQ ID NO: 5, Aminosäurepositionen 3191-3376 codieren eine Ketoreduktase-Domäne;
- Nucleotidpositionen 49182-49412 der SEQ ID NO: 5, Aminosäurepositionen 3459-3535 codieren eine β -Ketoacyl:Acyl Carrier Protein-Domäne;
- Nucleotidpositionen 49482-50000 der SEQ ID NO: 5 und Nucleotidposition 1 bis 759 der SEQ ID NO: 6, Aminosäurepositionen 3559-3984 codieren eine β -Ketoacyl:Acyl Carrier Protein Synthase-Domäne;
- 20 Nucleotidpositionen 1084-2049 der SEQ ID NO: 6, Aminosäurepositionen 4093-4414 codieren eine Acyltransferase-Domäne;
- Nucleotidpositionen 2146-2697 der SEQ ID NO: 6, Aminosäurepositionen 4447-4630 codieren eine Dehydratase-Domäne;
- 25 Nucleotidpositionen 3604-4155 der SEQ ID NO: 6, Aminosäurepositionen 4933-5116 codieren eine Ketoreduktase-Domäne;
- Nucleotidpositionen 4420-4677 der SEQ ID NO: 6, Aminosäurepositionen 5205-5290 codieren eine β -Ketoacyl:Acyl Carrier Protein-Domäne;
- 30 Nucleotidpositionen 4864-5538 der SEQ ID NO: 6, Aminosäurepositionen 5353-5577 codieren eine Thioesterase-Domäne.

SEQ ID NOS: 52 und 53, ORF23:

Nucleotidposition 344 bis 1333 der SEQ ID NO: 51, 329 Aminosäuren;
das ableitbare Genprodukt ist eine dNDP-Glucose-4,6-Dehydratase.

5

SEQ ID NOS: 54 und 55, ORF24:

Nucleotidposition 1330 bis 2247 der SEQ ID NO: 51, 305 Aminosäuren;
das ableitbare Genprodukt ist eine dNDP-4-keto-6-Deoxyglucose-3,5-Epimerase.

10 Die an der Cyclisierung des 5, 6, 5- Tricyclus beteiligten Produkte des ORF 5 (SEQ
ID NO: 16) und des ORF 8 (SEQ ID NO: 22) sind aufgrund der ungewöhnlichen
Cyclisierungsreaktionen von besonderem Interesse. Daher beinhaltet die vorliegende
Erfindung insbesondere auch homologe Nucleinsäuren oder homologe Genprodukte.
Vorzugsweise zeigen diese homologen Genprodukte mindestens eine 50 %ige,
15 bevorzugt eine 60 %ige und besonders bevorzugt eine 70 %ige Identität auf Amino-
säureebene.

Weiterhin sind Antikörper Gegenstand der Erfindung, die spezifisch an die
vorstehend genannten Polypeptide binden. Die Herstellung solcher Antikörper erfolgt
20 auf die übliche Weise. Diese Antikörper können genutzt werden, um Expres-
sionsklone z.B. einer Genbank zu identifizieren, die die erfindungsgemäßen Nuclein-
säuren tragen.

Gegenstand der vorliegenden Erfindung sind auch Verfahren zum Herstellen der
25 erfindungsgemäßen Nucleinsäuren. Die erfindungsgemäßen Nucleinsäuren können
auf die übliche Weise hergestellt werden. Beispielsweise können die Nucleinsäure-
moleküle vollständig chemisch synthetisiert werden. Man kann auch kurze Stücke
der erfindungsgemäßen Nucleinsäuren chemisch synthetisieren und solche
Oligonucleotide radioaktiv oder mit einem Fluoreszenzfarbstoff markieren. Die
30 markierten Oligonucleotide können auch verwendet werden, um Genbanken von
Organismen zu durchsuchen. Klone, an die die markierten Oligonucleotide hybridi-

sieren, werden zur Isolierung der betreffenden DNA ausgewählt. Nach der Charakterisierung der isolierten DNA erhält man auf einfache Weise die erfindungsgemäßen Nucleinsäuren. Die erfindungsgemäßen Nucleinsäuren können auch mittels PCR-Verfahren unter Verwendung chemisch synthetischer Oligonucleotide hergestellt werden.

Gegenstand der vorliegenden Erfindung sind weiterhin Verfahren zum Herstellen der erfindungsgemäßen Polypeptide. Zur Herstellung der Polypeptide, die von den erfindungsgemäßen Nucleinsäuren codiert werden, können Wirtszellen, die zumindest eine der erfindungsgemäßen Nucleinsäuren enthalten, unter geeigneten Bedingungen kultiviert werden. Die gewünschten Polypeptide können danach auf übliche Weise aus den Zellen oder dem Kulturmedium isoliert werden. Die Polypeptide können auch in *in vitro*-Systemen hergestellt werden.

Das isolierte und charakterisierte Gencluster und benachbarte oder assoziierte DNA-Regionen stellen ein Target zur Steigerung der Spinosyn-Biosynthese durch genetische Manipulation, Über- oder Unterexpression von direkt oder indirekt an der Biosynthese involvierten Genen oder regulatorischen Sequenzen dar. Diese Manipulationen können sowohl in natürlichen Spinosyn-produzierenden Organismen als auch in gentechnisch hergestellten Spinosyn-produzierenden Organismen durchgeführt werden. Beispielsweise können ausgewählte ORF's unter die Kontrolle üblicher starker Promotoren wie dem *mel*-Promotor des Plasmides pIJ702 (John Innes Foundation, Norwich, UK, 1985) gestellt werden.

Durch die Klonierung und Identifizierung der Spinosyn-Biosynthesegene schafft die vorliegende Erfindung die genetische Basis, mittels molekulargenetischer Verfahren neue Spinosyn-Vorstufen und -Derivate herzustellen.

Der Ausdruck "Spinosyn-Vorstufen", wie er hierin verwendet wird, bezieht sich auf alle nachweisbaren und alle postulierbaren Biosynthesevorstufen von Spinosyn.

Der Ausdruck "Spinosyn-Derivate", wie er hierin verwendet wird, bezieht sich auf Strukturderivate aller bisher bekannten Spinosyne.

5 Gegenstand der vorliegenden Erfindung ist somit auch ein Verfahren zum Herstellen von Spinosyn-Vorstufen und -Derivaten.

Die erfindungsgemäßen Nucleinsäuren können beispielsweise eingesetzt werden, um durch kombinatorische Biosynthese neue Spinosyn-Derivate mit Veränderungen des Spinosyn-Aglycons herzustellen. Dies kann z.B. dadurch erreicht werden, dass die von ORF 19 codierte, eine Acetat-Einheit einbauende Acyltransferase-Domäne ausgetauscht wird gegen eine Acyltransferase-Domäne, die eine Propionat-Einheit einbaut. In gleicher Weise kann die, eine Acetat-Einheit einbauende Acyltransferase-Domäne des ORF 18 gegen eine Acyltransferase-Domäne ausgetauscht werden, die eine Propionat-Einheit einbaut. Ferner ist es möglich beide oder jeweils eine Ketoreduktase-Domäne, die von beiden genannten ORF's codiert werden zu inaktivieren, durch eine inaktive Ketoreduktase-Domäne zu ersetzen oder zu deletieren, wodurch eine Hydroxygruppe an der entsprechenden Position im Makrocyclus biosynthetisch hergestellt werden kann. Alle Acyltransferase-, Ketoreduktase-, Dehydratase-, Enoylreduktase-, β -Ketoacyl:Acyl Carrier Protein und Thioesterase-Domänen können einzeln oder in beliebiger Kombination durch entsprechende Polyketidsynthase-Domänen mit anderer Substrat- oder Reaktionsspezifität ersetzt werden, in beliebiger Kombination miteinander fusioniert, einzeln oder in beliebiger Kombination mutagenisiert, deletiert oder dupliziert werden. Ferner können Modulcodierende Sequenzen ausgetauscht werden. So ist es denkbar die Modul 2-codierende DNA-Sequenz (Abb. 6) gegen die Modul 1- oder Modul 3, 4, 5, 6, 7, 8- oder Modul 9-codierende DNA-Sequenz (Abb. 6) zu ersetzen und funktionell zu exprimieren. Es ist auch denkbar die Modul 2-codierende DNA-Sequenz oder jede andere Modul-codierende DNA-Sequenz des Spinosyn-Polyketidsynthase-Genclusters gegen eine andere Modul-codierende DNA-Sequenz des Spinosyn-Polyketidsynthase-Genclusters, die eine andere biosynthetische Verlängerungseinheit einbaut, auszutauschen. Darüber hinaus kann jede andere Modul-codierende DNA-

Sequenz des Spinosyn-Polyketidsynthase-Genclusters gegen eine andere Modul-
codierende DNA-Sequenz einer anderen Polyketidsynthase-Nukleinsäuresequenz aus
S. spinosa oder einem anderen Organismus als *S. spinosa*, wie z.B.
Saccharopolyspora erythraea, ausgetauscht werden. Diese Veränderungen können
5 unter Ausnutzung der ET-Rekombination (WO 99/29837; Muyrers et al., 1999) oder
anderer Klonierungs- und Rekombinationstechniken durchgeführt werden.

Gegenstand der Erfindung sind somit auch alle Modul- oder Domänen-codierenden
Nucleinsäuren, die natürlicher oder gentechnisch erzeugter Bestandteil der Spinosyn-
Polyketidsynthase sind.
10

Der Ausdruck "Modul", sowie er hierin verwendet wird, bedeutet, dass eine Anord-
nung von drei enzymkatalytisch aktiven Domänen vorliegt, die zu eine Verlängerung
der wachsenden Polyketidkette um eine biosynthetische Verlängerungseinheit
führen. Bei diesen Domänen handelt es sich um eine β -Ketoacyl:Acyl Carrier Protein
15 Synthase-Domäne, eine Acyltransferase-Domäne und eine β -Ketoacyl:Acyl-Carrier
Protein-Domäne. Ein Modul kann auch eine Ketoreduktase-, eine Dehydratase-, eine
Enoylreduktase- und eine Thioesterase-Domäne tragen. Ein sog. Ladungsmodul, das
am Beginn der Biosynthese steht kann von den genannten Domänen lediglich eine
20 Acyltransferase-Domäne und eine β -Ketoacyl:Acyl-Carrier Protein-Domäne tragen,
sowie eine enzymatisch inaktive β -Ketoacyl:Acyl Carrier Protein Synthase-Domäne.
Eine Polyketidsynthase-Domäne umfasst jeweils eine dieser genannten enzyma-
tischen Aktivitäten.

25 Die erfindungsgemäßen Nucleinsäuren können weiterhin genutzt werden, um im
Zuge einer kombinatorischen Biosynthese durch Neuordnung und Expression von
Spinosyn-Polyketidsynthase-Nucleinsäuresequenzen oder durch Kombination und
Expression zusammen mit Polyketidsynthase-Nucleinsäuresequenzen einer anderen
Polyketidsynthase codierenden Nucleinsäuresequenz aus *S. spinosa* oder einem
30 anderen Organismus, wie z.B. *Saccharopolyspora erythraea*, Bibliotheken von re-
kombinanten Polyketidsynthase-Nucleinsäuresequenzen, rekombinanten Polyketid-

5 synthase-Proteinen oder rekombinant erzeugten Polyketiden herzustellen. Diese Polyketide können durch die Verwendung der erfindungsgemäßen Nucleinsäuren oder die Verwendung anderer Nucleinsäuren, deren ableitbaren Produkte an der Biosynthese anderer Zucker und Ankopplung ans Aglycon beteiligt sind, glycosyliert werden. Es ist bekannt, dass die Glycosylierung des Aglycons eine entscheidende Rolle bei der biologischen Aktivität am Wirkort spielt. Diese Veränderungen können sowohl in natürlichen als auch in gentechnisch hergestellten Spinosyn-produzierenden Organismen, insbesondere Bakterien, erfolgen. Weiterhin können diese Veränderungen unter Ausnutzung der ET-Rekombination (WO 99/29837; Muyrers et al., 10 1999) oder anderer Klonierungs- und Rekombinationstechniken durchgeführt werden.

15 Die erfindungsgemäßen Nucleinsäuren, Vektoren und regulatorischen oder genetisch mobilen Regionen können außerdem zum Auffinden von Genen verwendet werden, die für Polypeptide codieren, welche funktionell ähnliche Polyketidsynthasen oder funktionell ähnliche Produkte, die an einer Zuckerbiosynthese beteiligt sind, codieren.

20 Da die erfindungsgemäßen Nucleinsäuren einen umfangreichen Teil des Genoms von *S. spinosa* ausmacht, können die erfindungsgemäßen Nucleinsäuren als Marker bei der Sequenzierung des Genoms von *S. spinosa* eingesetzt werden, wodurch die Anordnung von Teilsequenzen eines Genomsequenzierungsprojektes erheblich erleichtert wird.

25 Somit liefern die erfindungsgemäßen Nucleinsäuren Daten, die im Rahmen eines Genomsequenzierungsprojektes und eines sich darauf aufbauenden Metabolic Engineering zur Steigerung der Spinosynproduktion eingesetzt werden können.

Erläuterungen zu den Abbildungen:

Abbildung 1: Modell für die Biosynthese der Spinosyn-Zucker D-Forosamin und 2, 3, 4-Tri-O-Methyl-L-Rhamnose.

5

Abbildung 2: Lage, der an der Spinosyn-Biosynthese direkt oder indirekt beteiligten DNA-Regionen 1 (SEQ ID NO: 4) und DNA-Region 2 (SEQ ID NOS: 5 und 6). Die schwarzen Balken im unteren Teil der Abbildung geben schematisch die Positionen der Cosmid-DNA Inserts zueinander und in Bezug zu den DNA-Regionen 1 und 2 an. Die dargestellten Cosmid-Inserts wurden zur Sequenzierung der SEQ ID NOS: 1 bis 3 herangezogen.

10

Abbildung 3: Schematische Darstellung der Lage der Insert-DNA (schwarze Balken im unteren Teil der Abbildung) der benannten Cosmide, die zur Ankopplung eines Forosamin-Restes oder eines Trimethyl-Rhamnose-Restes durch Biotransformation des Spinosyn-Aglycons und Spinosyn-Pseudoaglycons herangezogen worden sind.

15

Abbildung 4: Schematische Darstellung der offenen Leserahmen (ORF's) der DNA-Region 3, die der SEQ ID NO: 51 entspricht, auf Cosmid 16-2-2.

20

Abbildung 5: Schematische Darstellung offener Leserahmen (ORF's) der DNA-Regionen 1 und 2. Die ORF's sind nummeriert von 1 bis 22 entsprechend SEQ ID NOS: 7, 9, 11, 13, 15, 17, 19, 21, 23, 25, 27, 29, 31, 33, 35, 37, 39, 41, 43, 45, 47 und 49.

25

Abbildung 6: Schematische Darstellung offener Leserahmen (ORF's) der DNA-Region 2 (SEQ ID NOS: 5 und 6) und ableitbarer Module und Domänen. SM, Startmodul; M1 bis M10, Modul 1 bis Modul 10; KS, β -Ketoacyl:Acyl Carrier Protein Synthase; AT, Acyltransferase; ACP, β -Ketoacyl:Acyl Carrier Protein; KR, Ketoreduktase; DH, Dehydratase; ER, Enoylreduktase; TE, Thioesterase.

30

Abbildung 7: Schematische Darstellung der Lage von BAC-Shuttleklon Insert-DNA als schwarze Balken im unteren Teil der Abbildung. Die Größe der Insert-DNA beträgt mindestens 100 kb. Durchgezogene Balken: DNA-Sequenz ist identisch mit Teilen der DNA-Region 1 und der Gesamtheit der DNA-Region 2 (P11/G6 und P11/B10) bzw. mit der Gesamtheit der DNA-Region 1 und Teilen der DNA-Region 2 (P8/G11). Gestrichelte Balken: DNA-Sequenz liegt außerhalb des sequenzierten Bereichs.

Beispiele

Bakterienstämme und Plasmide

5 *Escherichia coli* XL1-Blue MRF' und die Cosmidvektoren SuperCos1 (Stratagene, Europe) und pOJ446 (Biermann et al., 1992) wurden verwendet zur Erstellung von Genbanken von *S. spinosa* ATCC49460 (American Type Culture Collection, U.S.A., EP-A 0 375 316). *E. coli* JM110 (Stratagene, Europe) wurde verwendet zur Propa-
gierung von Plasmiden, die durch Transformation nach *Streptomyces* übertragen wurden. *Streptomyces albus* J1074 (Chater and Wilde, 1980; John Innes Institut in
10 Norwich, UK) wurde zur heterologen Expression von und zur Biotransformation mit Spinosyn-Biosynthesegenen eingesetzt.

Plasmid pBeloBAC11 (Kim et al., 1996) und pOJ446 (Biermann et al., 1992) wurden
verwendet zur Herstellung eines *E. coli* – *Streptomyces* BAC-Shuttlevektors.

15

Molekularbiologische Methoden

Molekularbiologische Methoden wie DNA-Restriktion, Agarose-Gelelektrophorese von DNA, Ligation von Restriktionsfragmenten, Kultivierung und Transformation
20 von *E. coli* wurden durchgeführt wie beschrieben in Sambrook et. al (1989). Plasmide wurden mit Qiagen Plasmid Kit (Qiagen, Hilden, Deutschland) isoliert. Die verwendeten Enzyme stammten von Roche Diagnostics GmbH (Mannheim, Deutschland).

25 Anzucht Bedingungen and molekulargenetische Methoden mit *S. spinosa* und Streptomyceten sind beschrieben in (Hopwood et al., 1985). Alle Anzuchten in Flüssigkultur von *S. spinosa* oder Streptomyceten erfolgten aerob in Erlenmeyerkolben bei 28°C.

Die DNA-DNA-Hybridisierungen erfolgten unter Verwendung des DIG-High Prime DNA Labeling and Detection Kit nach Angaben des Herstellers (Roche Diagnostics GmbH, Mannheim, Deutschland).

5 Wachstumsmedien:

LB Sambrook et. al., 1989

TS Difco Bestell-Nummer 0 370-17-3 (Difco Detroit, MI, USA)

10

R5A Illing et al., 1985

Herstellung einer Cosmid Genbank von *S. spinosa*

15 Um eine Genbank von *S. spinosa* zu erhalten, wurde chromosomale DNA von *S. spinosa* ATCC49460 mit *Mbo*I partiell geschnitten und durch Zentrifugation im Glucosedichtegradienten aufgetrennt. Die Cosmid-DNA (SuperCos1, Stratagene Europe) wurde nach Angaben des Herstellers vorbereitet, mit den *S. spinosa* DNA-Fragmenten zwischen 35 und 45 kb ligiert und mit Hilfe des Gigapack-Verpackungs-
20 system (Stratagene Europe) in Phagenpartikel verpackt. Die Transfektion erfolgte in *E. coli* XL-1 blue MRF'. Diese Methode wurde ebenfalls dazu verwendet eine zweite *S. spinosa* Genbank anzulegen unter Verwendung des *E. coli-Streptomyces* Shuttle-Cosmids pOJ446.

25 Sequenzierung des Spinosynbiosynthese-Genclusters und eines DNA-Fragmentes das außerhalb dieses Clusters liegt, dessen Produkte aber an der Biosynthese von Spinosyn beteiligt sind

30 Die Insert-DNA der SuperCos1 Cosmide 16-1-8, 16-59-1, und 16-59-8 wurden sequenziert. Eine ca. 4 kb große Lücke zwischen den Cosmiden 16-59-1 und 16-1-8

wurde durch primer walking Sequenzierung eines entsprechenden Teilbereiches von Cosmid 16-59-6 geschlossen.

5 Eine ca. 2,3 kb große DNA-Sequenz auf dem SuperCos1 Cosmid 16-2-2 wurde sequenziert.

Identifizierung und Charakterisierung von chromosomalen DNA-Fragmenten einer BAC-Shuttlevektor-Genbank aus *S. spinosa*, die Spinosyn-Biosynthesegensequenzen tragen

10

Zur Herstellung des BAC-Shuttlevektors, der nicht nur in *E. coli* sondern auch in Actinomyceten wie *Streptomyces* übertragen und vermehrt werden kann, wurde der Vektor pBeloBAC11 mit *Xho*I linearisiert, und durch die Anwendung von Klenow Polymerase wurden glatte DNA-Enden hergestellt. Ein ca. 6 kb großes *Dra*I –
15 *Eco*RV DNA-Fragment des Cosmidvektors pOJ446, das den Replikationsursprung des Plasmides SCP2*, das Apramycinresistenzgen sowie den *oriT* zum konjugativen Transfer trägt, wurde mit dem linearisierten BAC-Vektor ligiert. Der resultierende Vektor erhielt die Bezeichnung pEBZ333.

20 Ausgehend von partiell mit *Mbo*I geschnittener genomischer DNA des Stammes *S. spinosa* ATCC49460 und dem mit *Bam*HI geschnittenen Vektor pEBZ333 wurde eine BAC-Genbank erstellt.

Analyse und Annotation offener Leserahmen direkt oder indirekt an der Spinosyn-Biosynthese beteiligter DNA-Sequenzen

25

Ausgehend von der Sequenz gemäß SEQ ID NOS: 1 bis 3 wurden offene Leserahmen (ORF's) identifiziert, die direkt oder indirekt an der Biosynthese von Spinosyn beteiligt sind. Diese ORF's wurden in zwei DNA-Regionen unterteilt, die
30 als DNA-Region 1 und DNA-Region 2 (Abb. 2 und 5) bezeichnet werden und die Sequenzen gemäß SEQ ID NO: 4 bzw. 5 und 6 tragen. Die DNA-Region 1 trägt

offene Leserahmen, deren Produkte an der Modifizierung und Tricyclusbildung des Spinosyn-Aglycons beteiligt sind, während die DNA-Region 2 (Abb. 2, 5 und 6) offene Leserahmen umfasst, deren Produkte die Spinosyn-Polyketidsynthase codieren. Die beiden jeweils ersten Nucleotide dieser DNA-Regionen liegen unmittelbar nebeneinander (Abb. 2, 3 und 5).

Eine weitere DNA-Region 3 (SEQ ID NO: 51) liegt außerhalb dieses Clusters von DNA-Sequenzen und trägt offene Leserahmen, deren Produkte ebenfalls an der Biosynthese des Spinosyn-Zuckers Trimethyl-Rhamnose beteiligt sind.

Herstellung des Spinosyn-Aglycons und 17-Pseudoaglycons aus Tracer®

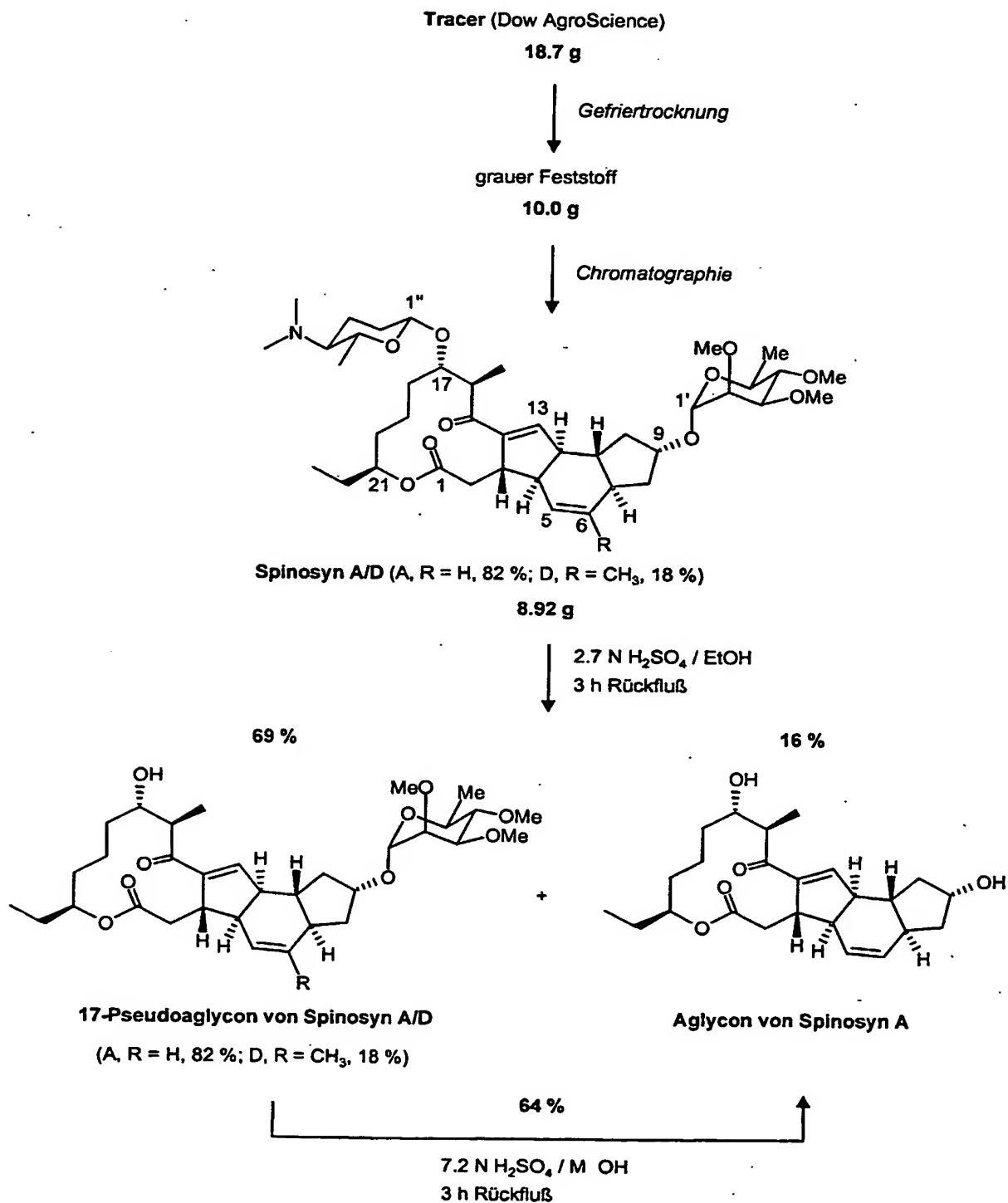
Ausgehend von 18,7 g des kommerziell erhältlichen Produktes Tracer® wurden nach Gefriertrocknung und Säulenchromatographie an Kieselgel 8,92 g Spinosyn A und D in einem Verhältnis von 82:18 gewonnen.

Die Hydrolyse des Aminosuckers Forosamin gelang mit 2.7 N Schwefelsäure in Ethanol unter Rückfluß. Dabei fiel der Großteil des entstehenden 17-Pseudoaglycons von Spinosyn A/D aus. Im Filtrat wurden neben weiterem 17-Pseudoaglycon in Abhängigkeit von der Reaktionsdauer geringe bis mittlere Mengen des Spinosyn-Aglycons gefunden.

Eine vollständige Hydrolyse zum Aglycon gelang unter etwas drastischeren Bedingungen (7.2 N Schwefelsäure in Methanol unter Rückfluß). Die Aglycon-Fraktion enthielt ausschließlich Aglycon von Spinosyn A. Dies stimmt sehr gut mit der Literatur überein (Creemer et al., 1998), die unter entsprechenden Reaktionsbedingungen eine vollständige Zersetzung des Pseudoaglycons von Spinosyn D beschreibt. Als Ursache nehmen die Autoren eine leichtere Protonierung der 5,6-Doppelbindung bei Spinosyn D unter Bildung eines tertiären Carbokations und anschließende Umlagerungen an.

- 29 -

Es konnten somit ausgehend von 18,7 g käuflichem Tracer[®] 3,0 g Aglycon von Spinosyn A hergestellt werden.



Gewinnung von Spinosyn A/D aus Tracer®

Die Gefriertrocknung von 18,7 g Tracer® lieferten 10,0 g grauen Feststoff. Nach Säulenchromatographie dieses Feststoffes an 800 cm³ Kieselgel (Eluent: Dichlormethan/Methanol 95:5) erhielt man 8,92 g reines Spinosyn A/D (82 % A, 18 % D).
5 – DC: R_f (SiO₂, Dichlormethan/Methanol 9:1) = 0,46. – ¹H-NMR: CDCl₃, δ = 6,77 (s, 13-H); 5,88 (d, 5-H von Spinosyn A); 5,80 (m, 6-H von Spinosyn A); 5,49 (m, 5-H von Spinosyn D); 4,87 (d, 1'-H); 4,67 (m, 21-H); 4,43 (d, 1''-H); 4,31 (m, 9-H) u. a. – LC/MS: Elektrospray Positiv; Peak bei RT 44,0 min: m/z = 733 (100 %) [M+H]⁺ (Spinosyn A); Peak bei 44,7 min: m/z = 747 (100 %) [M+H]⁺ (Spinosyn D).
10

Darstellung des 17-Pseudoaglycons von Spinosyn A/D:

8,65 g (11,81 mmol) Spinosyn A/D wurden in 61 ml Ethanol gelöst und mit 104 ml
15 Wasser und 208 ml 4 N H₂SO₄ versetzt. Nach 3 h Erwärmen unter Rückfluß wurde der ausgefallene Feststoff (A) abfiltriert und getrennt vom Filtrat (B) aufgearbeitet. Der Feststoff (A) wurde mit 1 N H₂SO₄ gewaschen, in 140 ml Dichlormethan aufgenommen, nacheinander mit gesätt. NaHCO₃-Lösung und gesätt. NaCl-Lösung gewaschen, über Na₂SO₄ getrocknet und im Vakuum eingeengt. Umkristallisation aus
20 Ethanol lieferten 3,03 g 17-Pseudoaglycon von Spinosyn A/D und Mutterlauge (C). Das Filtrat (B) wurde mehrmals mit Dichlormethan extrahiert. Die Extrakte wurden nacheinander mit gesätt. NaHCO₃-Lösung und gesätt. NaCl-Lösung gewaschen, über Na₂SO₄ getrocknet und im Vakuum eingeengt. Der Rückstand wurde vereint mit der im Vakuum eingeengten Mutterlauge (C) und durch Säulenchromatographie an
25 650 cm³ Kieselgel (Eluent: Cyclohexan/Essigsäureethylester 1:1, dann 100 % Essigsäureethylester) aufgetrennt. Man erhielt neben weiteren 1,76 g 17-Pseudoaglycon von Spinosyn A/D 0,78 g (16 %) Aglycon von Spinosyn A. Die Gesamtausbeute von 17-Pseudoaglycon von Spinosyn A/D betrug 4,79 g (69 %). – a) 17-Pseudoaglycon von Spinosyn A/D (82 % A, 18 % D): DC: R_f (SiO₂, Essigsäureethylester) = 0,48.
30 – ¹H-NMR: CDCl₃, δ = 6,78 (s, 13-H); 5,88 (d, 5-H von Spinosyn A); 5,80 (m, 6-H von Spinosyn A); 5,49 (m, 5-H von Spinosyn D); 4,86 (d, 1'-H); 4,70 (m, 21-H);

4,32 (m, 9-H) u. a. - LC/MS: Elektrospray Positiv; Peak bei RT 40,7 min: $m/z = 609$ (100 %) $[M+NH_4]^+$, $m/z = 641$ (10 %) $[M+NH_4+CH_3OH]^+$ (Pseudoaglycon von Spinosyn A); Peak bei RT 41,4 min: $m/z = 623$ (100 %) $[M+NH_4]^+$, $m/z = 655$ (8 %) $[M+NH_4+CH_3OH]^+$ (Pseudoaglycon von Spinosyn D). – b) Aglycon von Spinosyn A: DC: R_f (SiO₂, Essigsäureethylester) = 0,29. – ¹H-NMR: CDCl₃, $\delta = 6,80$ (s, 13-H); 5,89 (d, 5-H); 5,80 (m, 6-H); 4,70 (m, 21-H); 4,44 (m, 9-H) u. a. - LC/MS: Elektrospray Positiv; Peak bei RT 36,8 min: $m/z = 420$ (100 %) $[M+NH_4]^+$, $m/z = 452$ (10 %) $[M+NH_4+CH_3OH]^+$.

10 Darstellung des Aglycon von Spinosyn A/D

4,30 g (7,29 mmol) Pseudoaglycon von Spinosyn A/D wurden in 190 ml Methanol gelöst und mit 285 ml 7,2 N H₂SO₄ versetzt. Nach 3 h Erwärmen unter Rückfluß wurde die abgekühlte Reaktionsmischung vorsichtig in 1700 ml gesättigte NaHCO₃-Lösung gegeben. Man extrahierte mit Diethylether, wusch die Extrakte nacheinander mit gesätt. NaHCO₃-Lösung und gesätt. NaCl-Lösung, trocknete über Na₂SO₄ und engte im Vakuum ein. Nach Säulenchromatographie dieses Feststoffes an 650 cm³ Kieselgel (Eluent: Cyclohexan/Essigsäureethylester 1:2, dann 100 % Essigsäureethylester) erhielt man 1,88 g (64 %) Aglycon von Spinosyn A. – DC: R_f (SiO₂, Essigsäureethylester) = 0,29. – ¹H-NMR: CDCl₃, $\delta = 6,80$ (s, 13-H); 5,89 (d, 5-H); 5,80 (m, 6-H); 4,70 (m, 21-H); 4,44 (m, 9-H) u. a. – LC/MS: Elektrospray Positiv; Peak bei RT 36,6 min: $m/z = 420$ (100 %) $[M+NH_4]^+$, $m/z = 452$ (14 %) $[M+NH_4+CH_3OH]^+$ (Aglycon von Spinosyn A).

25 Forosaminylierung des Spinosyn-Aglycons und Anknüpfung eines Trimethyl-Rhamnosezuckers an das Spinosyn-Aglycon durch Biotransformation mit einem rekombinanten *Streptomyces* Stamm, der Spinosyn-Zuckerbiosynthesegene heterolog exprimiert

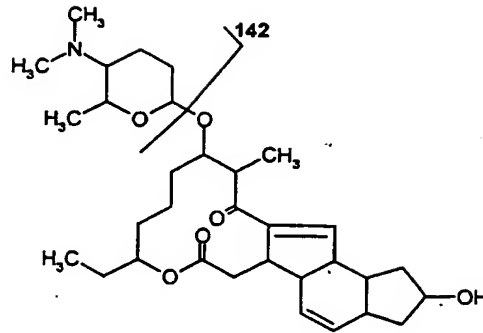
30 20 ml R5A Medium (Illing et al., 1989) mit 5 µg Apramycin / ml wurde mit Mycel des rekombinanten Stammes *S. albus* (165-1) oder *S. albus* (165-8) angeimpft und

24 h aerob bei 28°C bebrütet. Diese Kultur wurde mit 50 µg/ml des hergestellten Spinosyn-Aglycons (100 µl einer 1 %igen Stammlösung in Methanol; Herstellung siehe Kapitel "Herstellung des Spinosyn-Aglycons und 17-Pseudoaglycons aus Tracer[®]", „Gewinnung von Spinosyn A/D aus Tracer[®]“ und „Darstellung des Aglycon von Spinosyn A/D“) versetzt und ca. 120 h bei 28°C aerob inkubiert. Als Kontrolle wurde in gleicher Weise *S. albus* (pEBZ340; pOJ446-Vektor mit einem ca. 1,8 kb großen Spinosyn-PKS tragenden DNA-Fragment aus Cosmid 16-1-8) kultiviert und mit Spinosyn-Aglycon versetzt. Die Kulturen wurden nach Inkubation zur Abtrennung von Zellmycel zentrifugiert und der Überstand (20 ml) wurde mit 25 ml Methanol versetzt.

Je 35 ml des mit Methanol versetzten Kulturüberstandes wurden lyophilisiert, mit 15 ml Wasser aufgenommen und zweimal mit je 10 ml Essigsäureethylester extrahiert. Die vereinten organischen Phasen wurden zur Trockene eingengt und mit 350 µl Methanol aufgenommen. Ein Aliquot dieser Extrakte wurde mittels LC/MS mit Elektrospray Positiv-Ionisation untersucht.

Der Kulturüberstand der Anzucht von *S. albus* (165-1) enthielt eine Verbindung mit dem Molekulargewicht eines forosaminylierten Aglycons von Spinosyn A sowie Spinosyn A.

Peak 1: RT = 41,0 min: m/z = 544 (100 %) [M+H]⁺, m/z = 576 (16 %) [M+H+CH₃OH]⁺ (Forosaminyliertes Aglycon von Spinosyn A); LC/MS/MS: m/z = 142 (38 %) (Forosamin-Fragment).



Forosaminyliertes Aglycon von Spinosyn A
Molekulargewicht = 543
Summenformel = $C_{32}H_{49}NO_6$

Peak 2: RT = 44,2 min: $m/z = 733$ (100 %) $[M+H]^+$ (Spinosyn A); LC/MS/MS: $m/z = 142$ (21 %) (Forosamin-Fragment).

5

Der Kulturüberstand von *S. albus* (165-8) enthielt eine Verbindung mit dem Molekulargewicht eines Forosaminylierten Aglycons von Spinosyn A.

Peak 1: RT = 40,9 min: $m/z = 544$ (100 %) $[M+H]^+$, $m/z = 576$ (16 %) $[M+H+CH_3OH]^+$ (Forosaminyliertes Aglycon von Spinosyn A); LC/MS/MS: $m/z = 142$ (39 %) (Forosamin-Fragment).

10

Der Kulturüberstand von *S. albus* (pEBZ340) enthielt keine Verbindungen mit MW 543 und kein Spinosyn A.

15 Forosaminylierung des Spinosyn-17-Pseudoaglycons durch Biotransformation mit einem rekombinanten *Streptomyces* Stamm, der Spinosyn Zuckerbiosynthesegene heterolog exprimiert

20 ml R5A Medium (Illing et al., 1989) mit 5 μ g Apramycin / ml wurde mit Mycel des rekombinanten Stammes *S. albus* (165-1) oder *S. albus* (165-8) angeimpft und 24 h aerob bei 28°C bebrütet. Diese Kultur wurde mit 50 μ g/ml des hergestellten 17-Pseudoaglycons von Spinosyn (100 μ l einer 1 %igen Stammlösung in Methanol; Herstellung siehe Kapitel "Herstellung des Spinosyn-Aglycons und 17-Pseudoaglycons aus Tracer[®]", „Gewinnung von Spinosyn A/D aus Tracer[®]" und „Dar-

20

stellung des 17-Pseudoaglycon von Spinosyn A/D“) versetzt und ca. 120 h bei 28°C aerob inkubiert. Die Kulturen wurden nach Inkubation zur Abtrennung von Zellmycel zentrifugiert und der Überstand (20 ml) wurde mit 25 ml Methanol versetzt.

5

Je 35 ml des mit Methanol versetzten Kulturüberstandes wurden lyophilisiert, mit 15 ml Wasser aufgenommen und zweimal mit je 10 ml Essigsäureethylester extrahiert. Die vereinten organischen Phasen wurden zur Trockene eingeeengt und mit 350 µl Methanol aufgenommen. Ein Aliquot dieser Extrakte wurde mittels LC/MS mit Elektrospray Positiv-Ionisation untersucht.

10

Der Kulturüberstand von *S. albus* (165-1) enthielt Spuren von Spinosyn A und D.

Peak 1: RT = 44,2 min: m/z = 733 (100 %) [M+H]⁺ (Spinosyn A); LC/MS/MS: m/z = 142 (8 %) (Forosamin-Fragment).

15

Peak 2: RT = 44,7 min: m/z = 747 (100 %) [M+H]⁺ (Spinosyn D); LC/MS/MS: m/z = 142 (37 %) (Forosamin-Fragment).

Der Kulturüberstand von *S. albus* (165-8) enthielt Spuren von Spinosyn A und D.

Peak 1: RT = 44,1 min: m/z = 733 (100 %) [M+H]⁺ (Spinosyn A).

20

Peak 2: RT = 44,7 min: m/z = 747 (100 %) [M+H]⁺ (Spinosyn D).

Hinterlegung von Mikroorganismen

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Folgende Mikroorganismen und Plasmide sind bei der Deutschen Sammlung von Mikroorganismen und Zellkulturen GmbH (DSMZ), Mascheroder Weg 1b, D- 38124 Braunschweig, in Übereinstimmung mit den Bestimmungen des Budapester Vertrages hinterlegt worden.

	Mikroorganismus und Plasmid	Hinterlegungs- nummer	Datum
	<i>E. coli</i> XL1-Blue MRF' mit Cosmid 16-1-8	DSM 12961	1999-08-02
5	<i>E. coli</i> XL1-Blue MRF' mit Cosmid 16-2-2	DSM 12962	1999-08-02
	<i>E. coli</i> XL1-Blue MRF' mit Cosmid 16-59-1	DSM 12963	1999-08-02
	<i>E. coli</i> XL1-Blue MRF' mit Cosmid 16-59-6	DSM 12964	1999-08-02
	<i>E. coli</i> XL1-Blue MRF' mit Cosmid 16-59-8	DSM 12965	1999-08-02
	<i>E. coli</i> XL1-Blue MRF' mit Cosmid 165-1	DSM 13005	1999-08-18
10	<i>E. coli</i> XL1-Blue MRF' mit Cosmid 165-8	DSM 13007	1999-08-18
	<i>E. coli</i> DH10B mit dem BAC Shuttle-Klon P8 / G11	DSM 13012	1999-08-18
	<i>E. coli</i> DH10B mit dem BAC Shuttle-Klon P11 / B10	DSM 13011	1999-08-18
	<i>E. coli</i> DH10B mit dem BAC Shuttle-Klon P11 / G6	DSM 13010	1999-08-18
15	<u>Literatur</u>		
	Biermann M., Logan R., O'Brien K., Seno E.T., Nagaraja R., Schoner B.E. (1992) Plasmid cloning vectors for the conjugal transfer of DNA from <i>Escherichia coli</i> to <i>Streptomyces</i> spp. Gene 116: 43-49		
20	Chater K., Wilde L. (1980) <i>Streptomyces albus</i> G Mutants defective in the <i>SalGI</i> restriction-modification system. J. Gen. Microbiol. 116: 323-334.		
	Devereux J., Haeberli P., Smithies (1984) A comprehensive set of sequence analysis programs for the VAX. Nucleic Acids Research 12: 387-395.		
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Shizuya H., Birren B., Kim U.-J., Mancino V., Slepak T., Tachiiri Y., Simon M.I. (1992) Cloning and stable maintenance of 300-kilobase-pair fragments of human DNA in *Escherichia coli* using an F-factor-based vector. Proc. Natl. Acad. Sci. USA 89: 8794-8797.

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Smokvina T., Mazodier P., Bocard F., Thompson C.J., Guérineau M. (1990) Construction of a series of pSAM2-based integrative vectors for use in actinomycetes. Gene 94: 53-59.

Patentansprüche

1. Nucleinsäure, welche zumindest eine Region umfasst, die für eine Enzymaktivität codiert, welche an der Biosynthese von Spinosynen beteiligt ist.
2. Nucleinsäure gemäß Anspruch 1, dadurch gekennzeichnet, dass es sich um einzelsträngige oder doppelsträngige DNA oder RNA handelt.
3. Nucleinsäure gemäß Anspruch 2, dadurch gekennzeichnet, dass es sich um ein DNA-Fragment handelt.
4. Nucleinsäure gemäß Anspruch 3, dadurch gekennzeichnet, dass sie alle Regionen umfasst, die für Enzymaktivitäten codieren, welche an der Biosynthese von Spinosynen beteiligt sind.
5. Nucleinsäure gemäß einem der Ansprüche 1 bis 4, dadurch gekennzeichnet, dass es sich um Enzymaktivitäten von Polyketidsynthasen, Methyltransferasen, Glycosyltransferasen, Epimerasen, Aminotransferasen, Dimethyltransferasen, Reduktasen, Dehydratasen und/oder Cyclisierungsenzymen handelt.
6. Nucleinsäure gemäß einem der Ansprüche 1 bis 5, dadurch gekennzeichnet, dass sie aus *Saccharopolyspora spinosa* stammt.
7. Nucleinsäure gemäß Anspruch 1, umfassend zumindest eine Sequenz ausgewählt aus
 - (a) den Sequenzen gemäß SEQ ID NOS: 1, 2, 3, 4, 5, 6, 7, 9, 11, 13, 15, 17, 19, 21, 23, 25, 27, 29, 31, 33, 35, 37, 39, 41, 43, 45, 47, 49, 51, 52 oder 54,

- (b) zumindest 14 Basenpaare langen Teilsequenzen der unter (a) definierten Sequenzen,
- (c) Sequenzen, welche an die unter (a) definierten Sequenzen hybridisieren
- (d) Sequenzen, welche eine zumindest 70 %ige Identität zu den unter (a) definierten Sequenzen aufweisen,
- (e) Sequenzen, welche zu den unter (a) definierten Sequenzen komplementär sind, und
- (g) Sequenzen, welche aufgrund der Degeneriertheit des genetischen Codes für dieselbe Aminosäuresequenz kodieren wie die unter (a) bis (d) definierten Sequenzen.
8. Nucleinsäure gemäß Anspruch 7, dadurch gekennzeichnet, dass sie die Sequenz gemäß SEQ ID NOS: 1 bis 6 umfasst.
9. Nucleinsäure gemäß Anspruch 7, dadurch gekennzeichnet, dass sie die Sequenz gemäß SEQ ID NO: 4 umfasst.
10. Nucleinsäure gemäß Anspruch 7, dadurch gekennzeichnet, dass sie die Sequenz gemäß SEQ ID NOS: 5 und 6 umfasst.
11. Nucleinsäure gemäß Anspruch 7, dadurch gekennzeichnet, dass sie zumindest eine Sequenz gemäß SEQ ID NOS: 7, 9, 11, 13, 15, 17, 19, 21, 23, 25, 27, 29, 31, 33, 35, 37 oder 39 umfasst.
12. Nucleinsäure gemäß Anspruch 7, dadurch gekennzeichnet, dass sie zumindest eine Sequenz gemäß SEQ ID NOS: 41, 43, 45, 47 oder 49 umfasst.

13. Regulatorische Region, welche die Transkription einer Nukleinsäure gemäß einem der Ansprüche 1 bis 7 in *Saccharopolyspora spinosa* kontrolliert.
- 5 14. DNA-Konstrukt umfassend eine Nucleinsäure gemäß einem der Ansprüche 1 bis 12 und zumindest einen heterologen Promotor.
- 10 15. Vektor umfassend zumindest eine Nucleinsäure gemäß einem der Ansprüche 1 bis 12, eine regulatorische Region gemäß Anspruch 13 oder ein DNA-Konstrukt gemäß Anspruch 14.
- 15 16. Vektor gemäß Anspruch 15, dadurch gekennzeichnet, dass die Nucleinsäure funktionell mit regulatorischen Sequenzen verknüpft ist, welche die Expression der codierenden Regionen der Nucleinsäure in pro- oder eukaryotischen Zellen gewährleisten.
- 20 17. Vektor gemäß Anspruch 15 oder 16, dadurch gekennzeichnet, dass es sich um einen BAC-Vektor, PAC-Vektor oder einen zu BAC- oder PAC-Vektoren funktionell gleichwertigen Vektor handelt.
- 25 18. Vektor gemäß Anspruch 17, dadurch gekennzeichnet, dass es sich um einen Vektor handelt, der den BAC-Klonen mit den Hinterlegungsnummern DSM 13010, DSM 13011 oder DSM 13012 entspricht.
- 30 19. Vektor gemäß einem der Ansprüche 15 bis 18, dadurch gekennzeichnet, dass es sich um einen Shuttle-Vektor handelt, der sowohl in Prokaryonten als auch in Eukaryonten übertragbar ist.
20. Vektor gemäß einem der Ansprüche 15 bis 19, dadurch gekennzeichnet, dass es sich um einen Shuttle-Vektor handelt, der sowohl in Gram-negative und in Gram-positive Bakterien als auch in Archea übertragbar ist.

21. Vektor gemäß einem der Ansprüche 15 bis 19, dadurch gekennzeichnet, dass es sich um einen Shuttle-Vektor handelt, der sowohl in *Escherichia coli* als auch in Actinomyceten übertragbar ist.
- 5 22. Vektor gemäß Anspruch 21, dadurch gekennzeichnet, dass es sich um einen Shuttle-Vektor handelt, der sowohl in *Escherichia coli* als auch in *Streptomyces* übertragbar ist.
- 10 23. Vektor gemäß einem der Ansprüche 15 bis 22, dadurch gekennzeichnet, dass er in einem Prokaryonten autonom replizierbar ist.
24. Vektor gemäß einem der Ansprüche 15 bis 22, dadurch gekennzeichnet, dass er in einem Prokaryonten unter Beteiligung des Phagen Φ C31-, des pSAM2- oder des Mini-Circle-Integrationsmechanismus ins Genom integrierbar ist.
- 15 25. Vektor gemäß einem der Ansprüche 15 bis 22, dadurch gekennzeichnet, dass er in einem Prokaryonten durch RecA-vermittelte Rekombination ins Genom integrierbar ist.
- 20 26. Vektor gemäß einem der Ansprüche 15 bis 22, dadurch gekennzeichnet, dass er in einem Prokaryonten durch RecE- und RecT-vermittelte Rekombination ins Genom integrierbar ist.
- 25 27. Wirtszelle enthaltend eine Nucleinsäure gemäß einem der Ansprüche 1 bis 12, eine regulatorische Region gemäß Anspruch 13, ein DNA-Konstrukt gemäß Anspruch 14 oder zumindest einen Vektor gemäß einem der Ansprüche 15 bis 26.
- 30 28. Wirtszelle gemäß Anspruch 27, dadurch gekennzeichnet, dass es sich um eine pro- oder eukaryotische Zelle handelt.

29. Wirtszelle gemäß Anspruch 28, dadurch gekennzeichnet, dass die prokaryotische Zelle zur Gruppe der Actinomyceten, bevorzugt zur Gruppe der Streptomyceten gehört.
- 5 30. Wirtszelle gemäß Anspruch 28, dadurch gekennzeichnet, dass die eukaryotische Zelle eine Pflanzenzelle ist.
- 10 31. Polypeptid, welches von einer Nucleinsäure gemäß einem der Ansprüche 1 bis 7 codiert wird.
32. Polypeptid gemäß Anspruch 31, dadurch gekennzeichnet, dass es die Aktivität einer Methyltransferase aufweist.
- 15 33. Polypeptid gemäß Anspruch 32, dadurch gekennzeichnet, dass es die Aminosäuresequenz gemäß SEQ ID NOS: 8, 12, 14, 18 oder 20, oder eine Teilsequenz davon aufweist.
- 20 34. Polypeptid gemäß Anspruch 31, dadurch gekennzeichnet, dass es die Aktivität einer Glycosyltransferase aufweist.
- 25 35. Polypeptid gemäß Anspruch 34, dadurch gekennzeichnet, dass es die Aminosäuresequenz gemäß SEQ ID NOS: 10 oder 30, oder eine Teilsequenz davon aufweist.
- 30 36. Polypeptid gemäß Anspruch 31, dadurch gekennzeichnet, dass es die Aktivität eines C-C verknüpfenden Enzyms, das Cyclisierungsreaktionen durchführt, aufweist.
37. Polypeptid gemäß Anspruch 36, dadurch gekennzeichnet, dass es die Aminosäuresequenz gemäß SEQ ID NO: 16 oder eine Teilsequenz davon aufweist.

38. Polypeptid gemäß Anspruch 31, dadurch gekennzeichnet, dass es die Aktivität eines Enzyms, das an Cyclisierungsreaktionen beteiligt ist, aufweist.
- 5 39. Polypeptid gemäß Anspruch 38, dadurch gekennzeichnet, dass es die Aminosäuresequenz gemäß SEQ ID NO: 22 oder eine Teilsequenz davon aufweist.
40. Polypeptid gemäß Anspruch 31, dadurch gekennzeichnet, dass es die Aktivität einer 2,3-Reduktase aufweist.
- 10 41. Polypeptid gemäß Anspruch 40, dadurch gekennzeichnet, dass es die Aminosäuresequenz gemäß SEQ ID NO: 24 oder eine Teilsequenz davon aufweist.
42. Polypeptid gemäß Anspruch 31, dadurch gekennzeichnet, dass es die Aktivität einer 2,3-Dehydratase aufweist.
- 15 43. Polypeptid gemäß Anspruch 42, dadurch gekennzeichnet, dass es die Aminosäuresequenz gemäß SEQ ID NO: 26 oder eine Teilsequenz davon aufweist.
- 20 44. Polypeptid gemäß Anspruch 31, dadurch gekennzeichnet, dass es die Aktivität einer Thioesterase aufweist.
45. Polypeptid gemäß Anspruch 44, dadurch gekennzeichnet, dass es die Aminosäuresequenz gemäß SEQ ID NO: 28 oder eine Teilsequenz davon aufweist.
- 25 46. Polypeptid gemäß Anspruch 31, dadurch gekennzeichnet, dass es die Aktivität einer 3,4-Dehydratase aufweist.
- 30 47. Polypeptid gemäß Anspruch 46, dadurch gekennzeichnet, dass es die Aminosäuresequenz gemäß SEQ ID NO: 32 oder eine Teilsequenz davon aufweist.

48. Polypeptid gemäß Anspruch 31, dadurch gekennzeichnet, dass es die Aktivität einer 4-Aminotransferase aufweist.
- 5 49. Polypeptid gemäß Anspruch 48, dadurch gekennzeichnet, dass es die Aminosäuresequenz gemäß SEQ ID NO: 34 oder eine Teilsequenz davon aufweist.
50. Polypeptid gemäß Anspruch 31, dadurch gekennzeichnet, dass es die Aktivität einer N-Dimethyltransferase aufweist.
- 10 51. Polypeptid gemäß Anspruch 50, dadurch gekennzeichnet, dass es die Aminosäuresequenz gemäß SEQ ID NO: 36 oder eine Teilsequenz davon aufweist.
52. Polypeptid gemäß Anspruch 31, dadurch gekennzeichnet, dass es die Aktivität einer 3,4-Reduktase aufweist.
- 15 53. Polypeptid gemäß Anspruch 52, dadurch gekennzeichnet, dass es die Aminosäuresequenz gemäß SEQ ID NO: 38 oder eine Teilsequenz davon aufweist.
54. Polypeptid gemäß Anspruch 31, dadurch gekennzeichnet, dass es die Aktivität eines Transkriptions-Regulators aufweist.
- 20 55. Polypeptid gemäß Anspruch 54, dadurch gekennzeichnet, dass es die Aminosäuresequenz gemäß SEQ ID NO: 40 oder eine Teilsequenz davon aufweist.
- 25 56. Polypeptid gemäß Anspruch 31, dadurch gekennzeichnet, dass es die Aktivität einer Polyketidsynthase aufweist.
- 30 57. Polypeptid gemäß Anspruch 56, dadurch gekennzeichnet, dass es die Aminosäuresequenz gemäß SEQ ID NOS: 42, 44, 46, 48 oder 50, oder eine Teilsequenz davon aufweist.

58. Polypeptid gemäß Anspruch 31, dadurch gekennzeichnet, dass es die Aktivität einer Glucose-Dehydratase aufweist.
59. Polypeptid gemäß Anspruch 58, dadurch gekennzeichnet, dass es die Aminosäuresequenz gemäß SEQ ID NO: 53 aufweist.
60. Polypeptid gemäß Anspruch 31, dadurch gekennzeichnet, dass es die Aktivität einer 3,5-Epimerase aufweist.
61. Polypeptid gemäß Anspruch 60, dadurch gekennzeichnet, dass es die Aminosäuresequenz gemäß SEQ ID NO: 55 aufweist.
62. Enzyme, die an Cyclisierungsreaktionen beteiligt sind, dadurch gekennzeichnet, dass sie die Aminosäuresequenz gemäß SEQ ID NO: 15 oder 22, oder eine Teilsequenz davon, welche zumindest noch eine Teilreaktion durchführen kann, umfassen oder eine mindestens 50 %ige Identität dazu auf Aminosäureebene aufweisen.
63. Antikörper, welcher spezifisch mit einem Polypeptid gemäß einem der Ansprüche 31 bis 62 reagiert.
64. Verfahren zur Herstellung einer Nucleinsäure gemäß einem der Ansprüche 1 bis 7, umfassend die folgenden Schritte:
- (a) Vollständige chemische Synthese auf an sich bekannte Weise oder
- (b) chemische Synthese von Oligonucleotiden, Markieren der Oligonucleotide, Hybridisieren der Oligonucleotide an DNA einer genomischen oder cDNA-Bank, die ausgehend von genomischer DNA bzw. mRNA aus *S. spinosa* hergestellt wurde, Selektieren von

positiven Klonen und Isolieren der hybridisierenden DNA aus positiven Klonen oder

- 5 (c) chemische Synthese von Oligonucleotiden und Amplifizierung der Ziel-DNA mittels PCR.

65. Verfahren zur Herstellung eines Polypeptids gemäß einem der Ansprüche 31 bis 62, umfassend die folgenden Schritte:

- 10 (a) Kultivieren einer Wirtszelle gemäß einem der Ansprüche 27 bis 30 unter Bedingungen, die die Expression der Nucleinsäure gemäß einem der Ansprüche 1 bis 7 gewährleisten, oder

- 15 (a1) Exprimieren einer Nucleinsäure gemäß einem der Ansprüche 1 bis 7 in einem *in vitro*-System, und

- (b) Gewinnen des Polypeptids aus der Zelle, dem Kulturmedium oder dem *in vitro*-System.

20 66. Verfahren zum Herstellen von Spinosyn, Spinosyn-Vorstufen oder Spinosyn-Derivaten umfassend die folgenden Schritte:

- 25 (a) Kultivieren einer Wirtszelle gemäß einem der Ansprüche 27 bis 30 unter Bedingungen, die die Expression der Nucleinsäure gemäß einem der Ansprüche 1 bis 7 gewährleisten und

- (b) Gewinnen des Spinosyns, der Spinosyn-Vorstufe oder des Spinosyn-Derivates aus der Zelle oder dem Kulturmedium.

30 67. Verfahren zum Herstellen von Spinosyn-Derivaten, einschließlich Spinosyn-Vorstufen, umfassend die folgenden Schritte:

- 5 (a) Austauschen zumindest einer Modul-codierenden Nucleinsäuresequenz gemäß Anspruch 7 gegen zumindest eine andere Modul-codierende Nucleinsäuresequenz gemäß Anspruch 7, oder
- (b) Austauschen zumindest einer Modul-codierenden Nucleinsäuresequenz gemäß Anspruch 7 gegen zumindest eine andere Modul-codierende Nucleinsäuresequenz aus *S. spinosa*, oder
- 10 (c) Austauschen zumindest einer Modul-codierenden Nucleinsäuresequenz gemäß Anspruch 7 gegen zumindest eine andere Modul-codierende Nucleinsäuresequenz aus einem anderen Organismus als *S. spinosa*, oder
- 15 (d) Austauschen zumindest einer Domänen-codierenden Nucleinsäuresequenz gemäß Anspruch 7 gegen zumindest eine andere Domänen-codierende Nucleinsäuresequenz gemäß Anspruch 7, oder
- 20 (e) Austauschen zumindest einer Domänen-codierenden Nucleinsäuresequenz gemäß Anspruch 7 gegen zumindest eine andere Domänen-codierende Nukleinsäuresequenz aus *S. spinosa*, oder
- 25 (f) Austauschen zumindest einer Domänen-codierenden Nucleinsäuresequenz gemäß Anspruch 7 gegen zumindest eine andere Domänen-codierende Nucleinsäuresequenz aus einem anderen Organismus als *S. spinosa*, oder
- 30 (g) Austauschen einer ersten Acyltransferase-codierenden Nucleinsäuresequenz gemäß Anspruch 7 gegen eine zweite Acyltransferase-codierende Nucleinsäuresequenz gemäß Anspruch 7, wobei die zweite

Acyltransferase eine unterschiedliche Substratspezifität aufweist als die erste Acyltransferase, oder

5 (h) Austauschen einer ersten Acyltransferase-codierenden Nucleinsäuresequenz gemäß Anspruch 7 gegen eine zweite Acyltransferase-codierende Nucleinsäuresequenz aus *S. spinosa*, wobei die zweite Acyltransferase eine unterschiedliche Substratspezifität aufweist als die erste Acyltransferase, oder

10 (i) Austauschen einer ersten Acyltransferase-codierenden Nucleinsäuresequenz gemäß Anspruch 7 gegen eine zweite Acyltransferase-codierende Nucleinsäuresequenz aus einem anderen Organismus als *S. spinosa*, wobei die zweite Acyltransferase eine unterschiedliche Substratspezifität aufweist als die erste Acyltransferase, oder

15 (j) Deletieren zumindest einer Domänen-codierender Nucleinsäuresequenz gemäß Anspruch 7, oder

20 (k) Integrieren zumindest einer Domänen-codierenden Nucleinsäuresequenz gemäß Anspruch 7 in eine Modul-codierende Nucleinsäuresequenz gemäß Anspruch 7, oder

25 (l) Mutagenisieren zumindest einer Domänen-codierenden Nucleinsäuresequenz gemäß Anspruch 7,

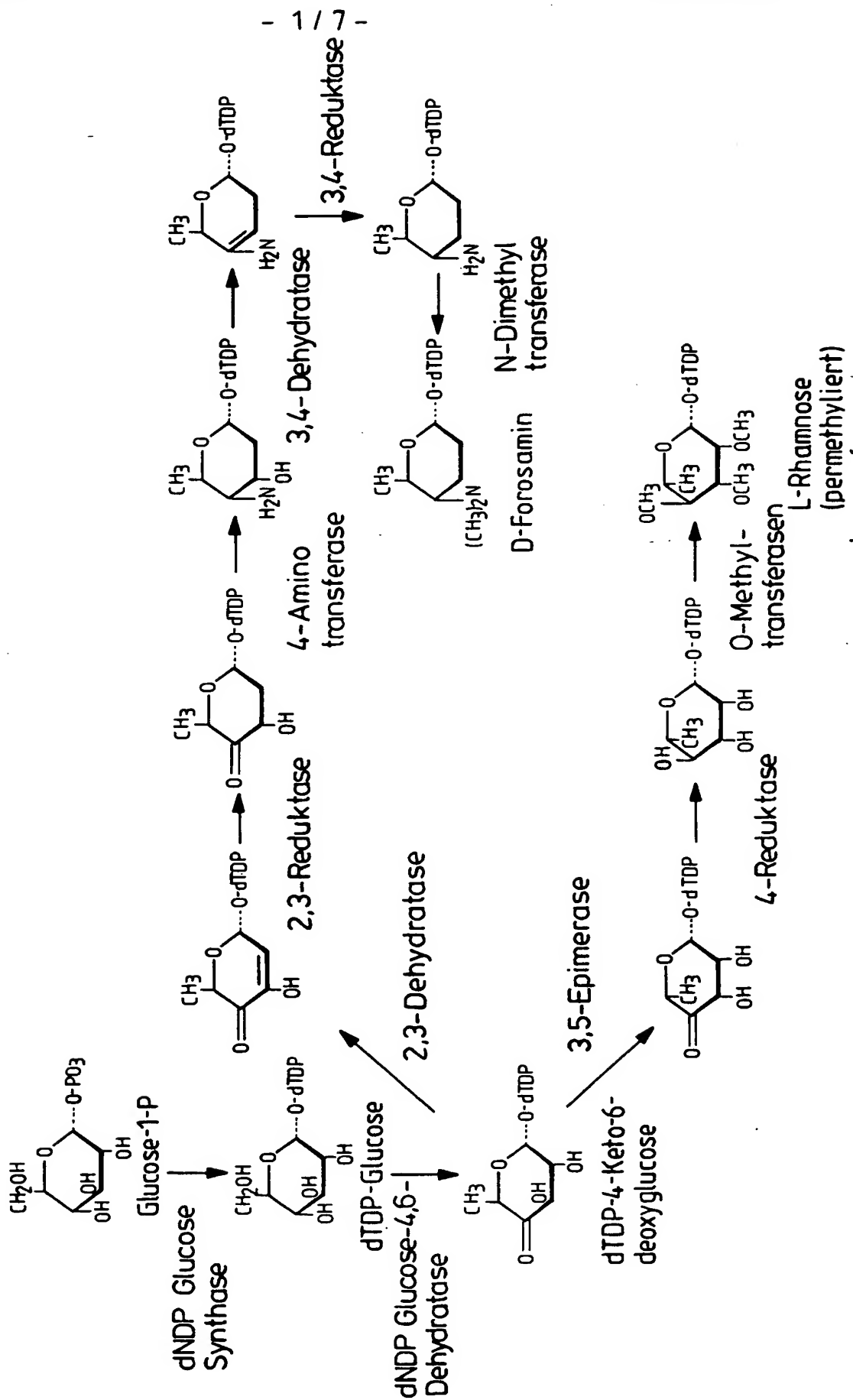
und Exprimieren der rekombinierten Nucleinsäuresequenz in einer Wirtszelle unter Bedingungen, welche die Synthese eines Spinosyn-Derivates oder einer Spinosyn-Vorstufe erlauben.

68. Verwendung einer Nucleinsäure gemäß einem der Ansprüche 1 bis 7 zum Identifizieren, Inaktivieren und/oder Modifizieren von Genen der Spinosyn-Biosynthese.
- 5 69. Verwendung einer Nucleinsäure gemäß einem der Ansprüche 1 bis 7 zum Erzeugen einer Bibliothek aus Polyketidsynthesen.
70. Verfahren zum Anfügen eines Forosamin-Zuckerrestes an das Spinosyn-Aglycon oder an das Spinosyn-17-Pseudoaglycon oder an ein Polyketid-Aglycon, umfassend die folgenden Schritte:
- 10
- (a) Übertragen einer Nucleinsäure gemäß SEQ ID NOS: 23, 25, 29, 31, 33, 35 und 37 in eine Wirtszelle, die das Spinosyn-Aglycon oder das Spinosyn-17-Pseudoaglycon oder das Polyketid-Aglycon herstellen kann, oder
- 15
- (a1) Übertragen einer Nucleinsäure gemäß SEQ ID NOS: 23, 25, 29, 31, 33, 35 und 37 in eine Wirtszelle, die das Spinosyn-Aglycon oder das Spinosyn-17-Pseudoaglycon oder das Polyketid-Aglycon nicht herstellen kann und Zufügen des Spinosyn-Aglycons oder des Spinosyn-17-Pseudoaglycons oder des Polyketid-Aglycons zum Kulturmedium, und
- 20
- (b) Kultivieren der Wirtszelle unter Bedingungen, die zu einem aktiven Stoffwechsel der Zelle führen.
- 25
71. Verfahren zum Anfügen eines Trimethyl-Rhamnose-Zuckerrestes an das Spinosyn-Aglycon oder an das Spinosyn-9-Pseudoaglycon oder an ein Polyketid-Aglycon, umfassend die folgenden Schritte:
- 30

- 5
- (a) Übertragen einer Nucleinsäure gemäß SEQ ID NO: 7, 9, 11, 13, 17 und/oder 19 in eine Wirtszelle, die das Spinosyn-Aglycon oder das Spinosyn-9-Pseudoaglycon oder das Polyketid-Aglycon herstellen kann, oder
- 10
- (a1) Übertragen einer Nucleinsäure gemäß SEQ ID NO: 7, 9, 11, 13, 17 und/oder 19 in eine Wirtszelle, die das Spinosyn-Aglycon oder das Spinosyn-9-Pseudoaglycon oder das Polyketid-Aglycon nicht herstellen kann und Zufügen des Spinosyn-Aglycons oder des Spinosyn-9-Pseudoaglycons oder des Polyketid-Aglycons zum Kulturmedium, und
- 15
- (b) Kultivieren der Wirtszelle unter Bedingungen, die zu einem aktiven Stoffwechsel der Zelle führen.
72. Verfahren gemäß Anspruch 71, dadurch gekennzeichnet, dass im Schritt (a) Nucleinsäuren gemäß SEQ ID NOS: 9, 11, 13 und 17 übertragen werden.

Fig. 1

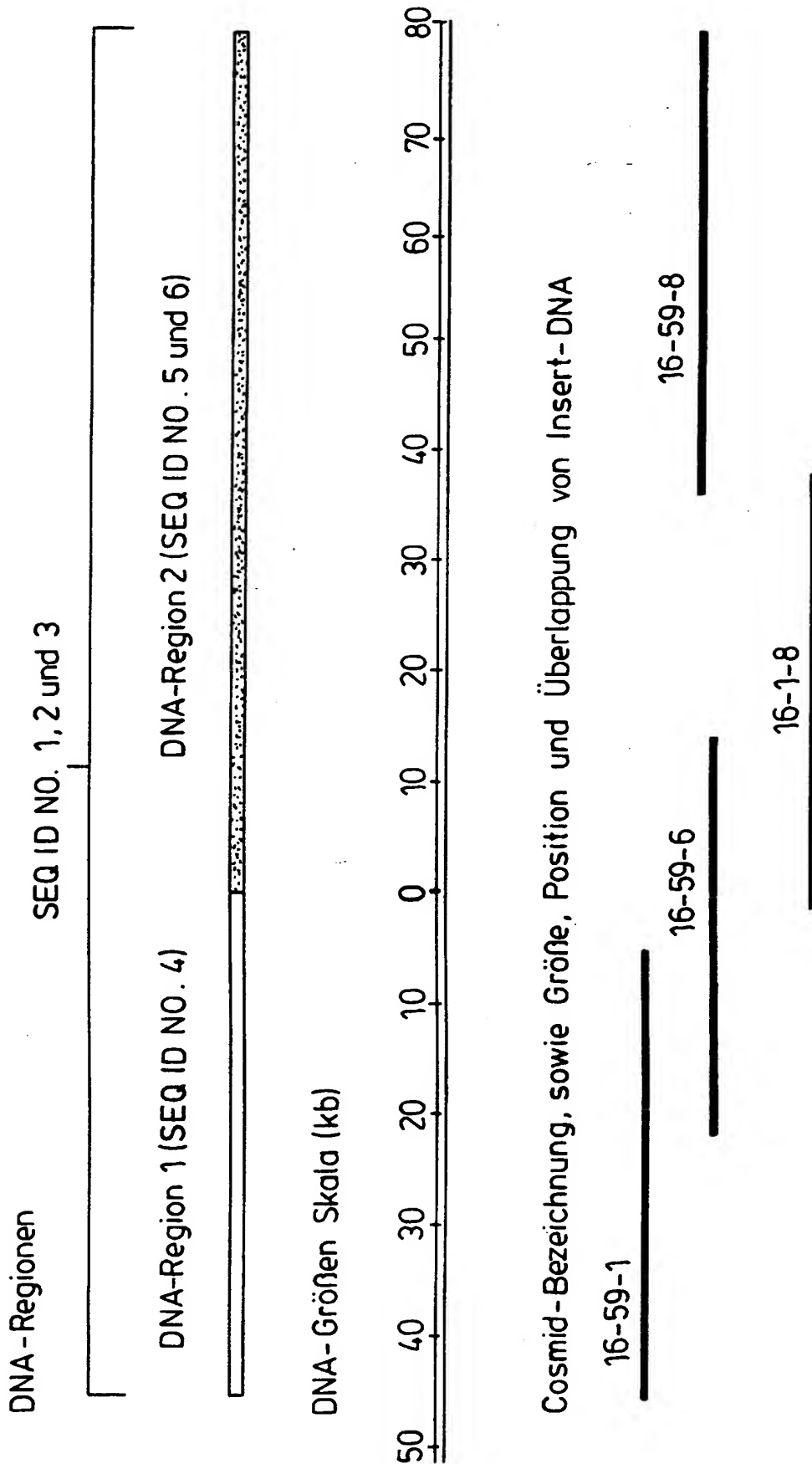
Modell für die Biosynthese der Spinosyn Zucker
D-Forosamin und 2,3,4-Tri-O-Methyl-L-Rhamnose



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Fig. 2

Lage, der an der Spinosyn Biosynthese direkt oder indirekt beteiligten DNA-Regionen 1 und 2 sowie Lage und Bezeichnung der zur Sequenzierung herangezogenen überlappenden Cosmidklone

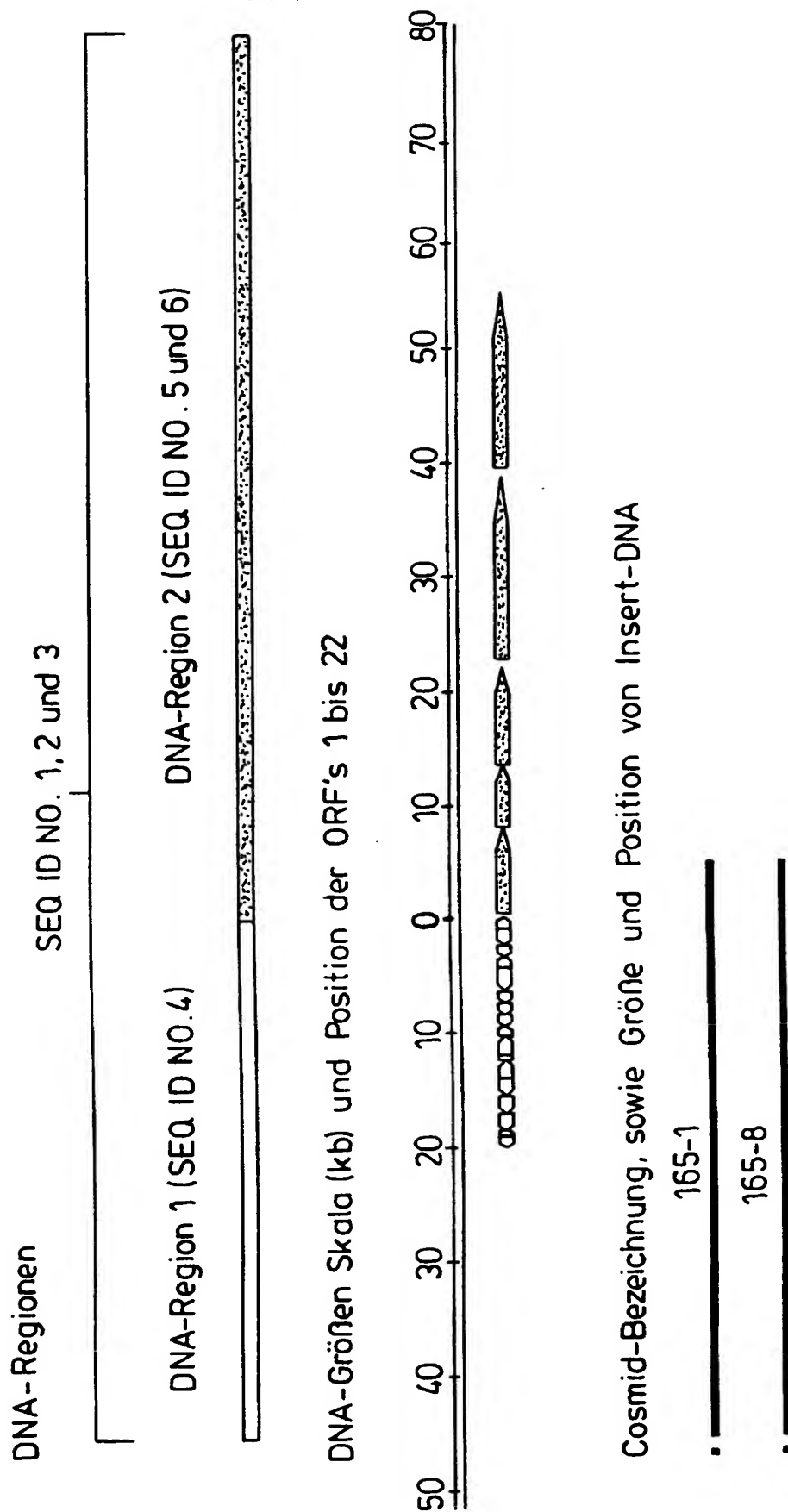


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- 3 / 7 -

Fig. 3

Zur Biotransformation herangezogene Cosmidklone



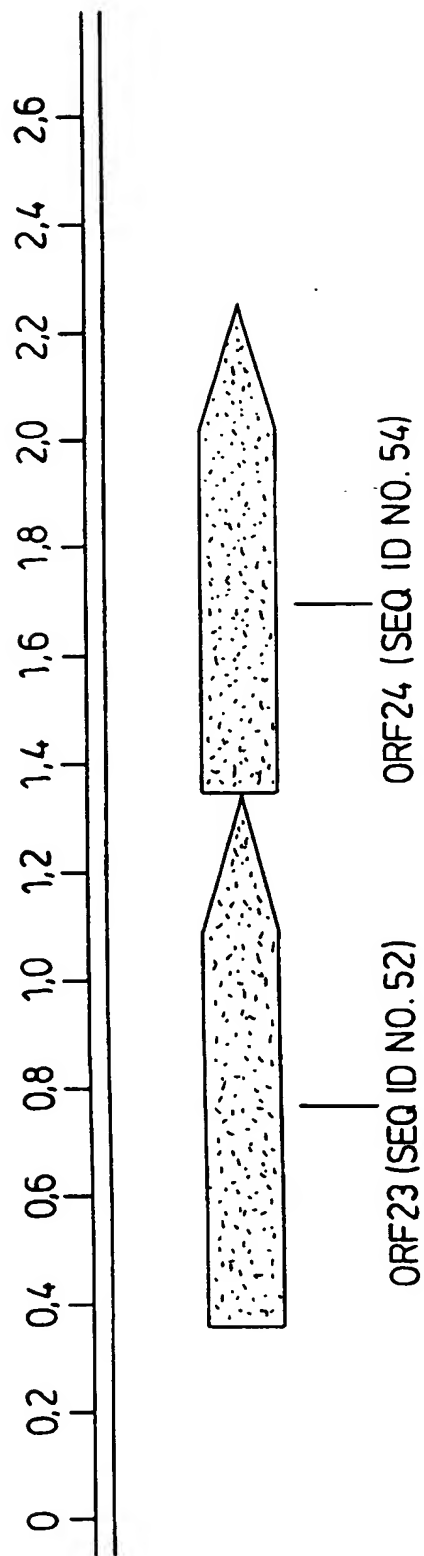
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Fig. 4

Darstellung offener Leserahmen der
DNA-Region 3 (SEQ ID NO. 51) auf Cosmid 16-2-2

SEQ ID NO. 51

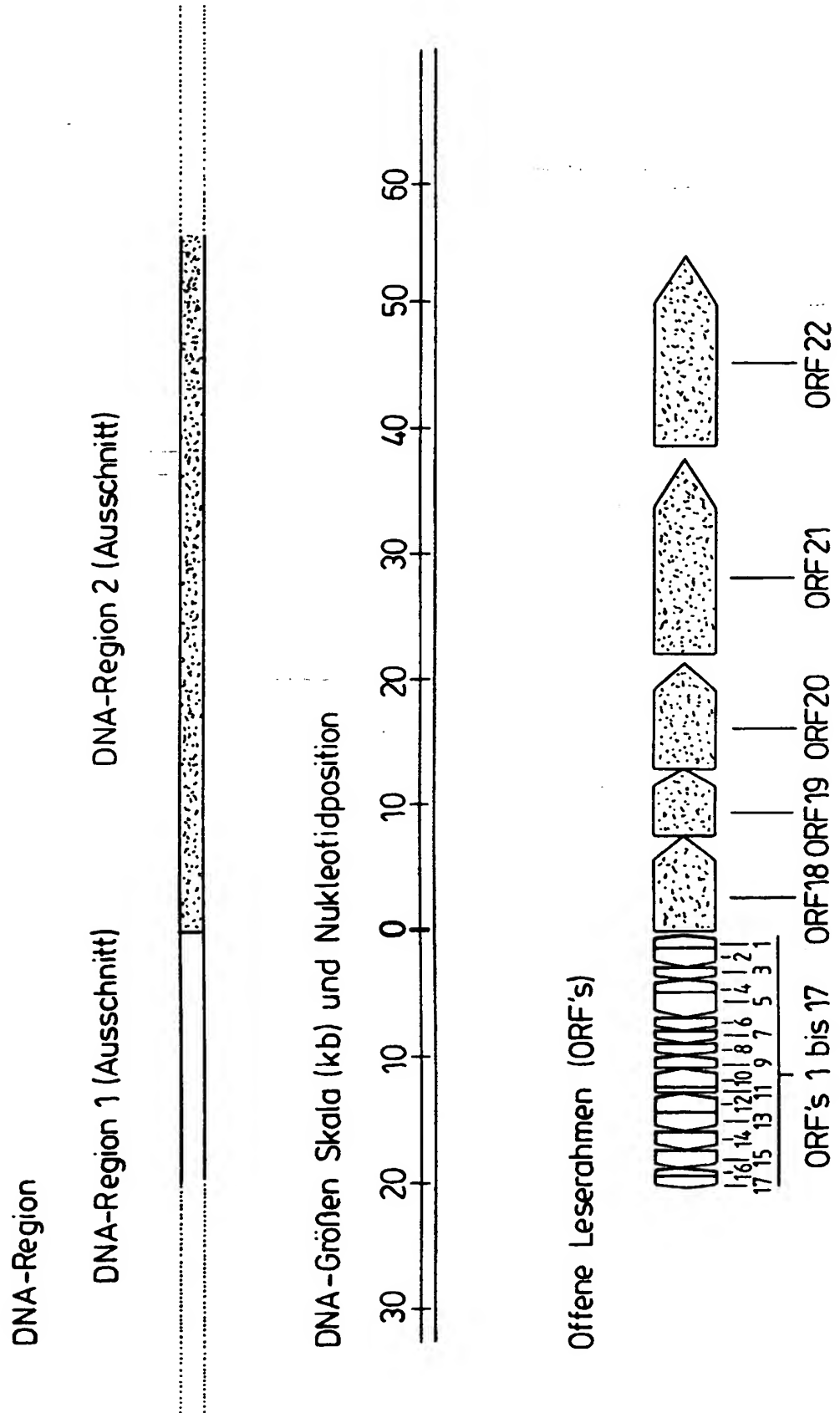
DNA-Größen Skala (kb) und Nukleotidposition



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Fig. 5

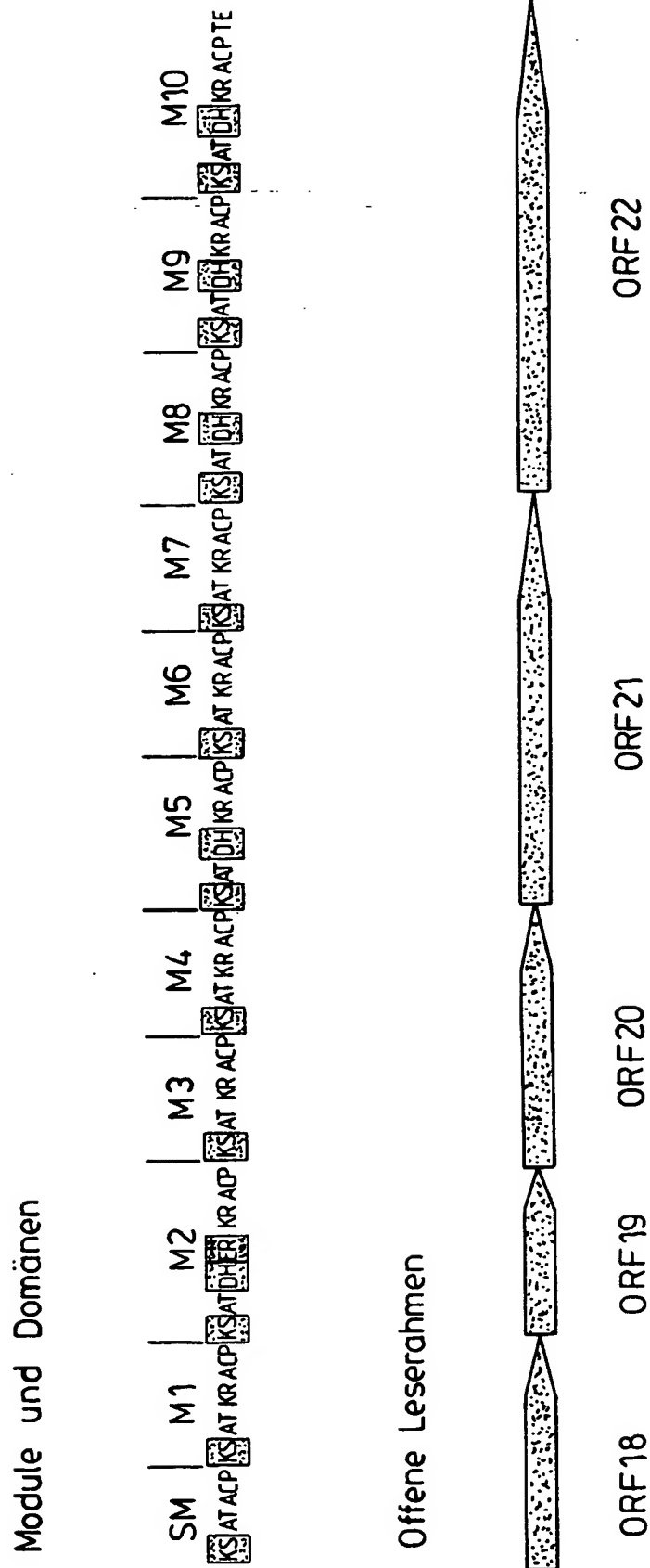
Darstellung offener Leserahmen der DNA-Regionen 1 und 2, die direkt oder indirekt an der Spinosyn-Biosynthese involviert sind



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Fig. 6

Darstellung offener Leserahmen der DNA-Region 2 und ableitbare Polyketidsynthese-Module und Domänen



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Fig. 7

Darstellung von Spinosyn Biosynthesegen BAC Shuttleklonen

DNA-Regionen

SEQ ID NO. 1, 2 und 3

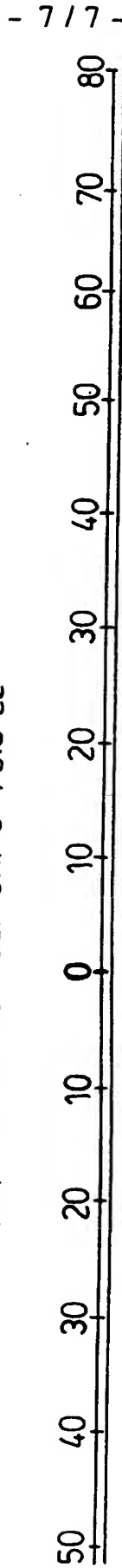


DNA-Region 1 (SEQ ID NO. 4)

DNA-Region 2 (SEQ ID NO. 5 und 6)



DNA-Größen Skala (kb) und Position der ORF's 1 bis 22



BAC Shuttleklon-Bezeichnung, sowie Größe und Position von Insert-DNA

P11/G6 (>100 kb)

P11/B10 (>100 kb)

P8/G11 (>100 kb)

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SEQUENZPROTOKOLL

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cag gcc cag tcc gac cac gaa cag ttc acc gac tca atc gca acg gtg 1056
Gln Ala Gln Ser Asp His Glu Gln Phe Thr Asp Ser Ile Ala Thr Val
340 345 350

ctc ggc gac acc ggc ttc gct gct gcg gca atc aaa ctc agc gac gag 1104
Leu Gly Asp Thr Gly Phe Ala Ala Ala Ala Ile Lys Leu Ser Asp Glu
355 360 365

atc acg gcc atg ccc cat ccc gcc gcg ctg gtg cgg acg ctg gag aac 1152
Ile Thr Ala Met Pro His Pro Ala Ala Leu Val Arg Thr Leu Glu Asn
370 375 380

act gcg gcc atc cgt gcc tga 1173
Thr Ala Ala Ile Arg Ala
385 390

<210> 10

<211> 390

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<212> PRT

<213> *Saccharopolyspora spinosa*

<400> 10

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Met Val Pro Leu Cys Trp Ala Leu Gln Ala Ser Gly His Glu Val Leu
 20 25 30

Ile Ala Ala Pro Pro Glu Leu Gln Ala Thr Ala His Gly Ala Gly Leu
 35 40 45

Thr Thr Ala Gly Ile Arg Gly Asn Asp Arg Thr Gly Asp Thr Gly Gly
 50 55 60

Thr Thr Gln Leu Arg Phe Pro Asn Pro Ala Phe Gly Gln Arg Asp Thr
 65 70 75 80

Glu Ala Gly Arg Gln Leu Trp Glu Gln Thr Ala Ser Asn Val Ala Gln
 85 90 95

Ser Ser Leu Asp Gln Leu Pro Glu Tyr Leu Arg Leu Ala Glu Ala Trp
 100 105 110

Arg Pro Ser Val Leu Leu Val Asp Val Cys Ala Leu Ile Gly Arg Val
 115 120 125

Leu Gly Gly Leu Leu Asp Leu Pro Val Val Leu His Arg Trp Gly Val
 130 135 140

Asp Pro Thr Ala Gly Pro Phe Ser Asp Arg Ala His Glu Leu Leu Asp
 145 150 155 160

Pro Val Cys Arg His His Gly Leu Thr Gly Leu Pro Thr Pro Glu Leu
 165 170 175

Ile Leu Asp Pro Cys Pro Pro Ser Leu Gln Ala Ser Asp Ala Pro Gln
 180 185 190

Gly Ala Pro Val Gln Tyr Val Pro Tyr Asn Gly Ser Gly Ala Phe Pro
 195 200 205

Ala Trp Gly Ala Ala Arg Thr Ser Ala Arg Arg Val Cys Ile Cys Met
 210 215 220

Gly Arg Met Val Leu Asn Ala Thr Gly Pro Ala Pro Leu Leu Arg Ala
 225 230 235 240

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Val Ala Ala Ala Thr Glu Leu Pro Gly Val Glu Ala Val Ile Ala Val
 245 250 255

Pro Pro Glu His Arg Ala Leu Leu Thr Asp Leu Pro Asp Asn Ala Arg
 260 265 270

Ile Ala Glu Ser Val Pro Leu Asn Leu Phe Leu Arg Thr Cys Glu Leu
 275 280 285

Val Ile Cys Ala Gly Gly Ser Gly Thr Ala Phe Thr Ala Thr Arg Leu
 290 295 300

Gly Ile Pro Gln Leu Val Leu Pro Gln Tyr Phe Asp Gln Phe Asp Tyr
 305 310 315 320

Ala Arg Asn Leu Ala Ala Ala Gly Ala Gly Ile Cys Leu Pro Asp Glu
 325 330 335

Gln Ala Gln Ser Asp His Glu Gln Phe Thr Asp Ser Ile Ala Thr Val
 340 345 350

Leu Gly Asp Thr Gly Phe Ala Ala Ala Ala Ile Lys Leu Ser Asp Glu
 355 360 365

Ile Thr Ala Met Pro His Pro Ala Ala Leu Val Arg Thr Leu Glu Asn
 370 375 380

Thr Ala Ala Ile Arg Ala
 385 390

<210> 11

<211> 753

<212> DNA

<213> *Saccharopolyspora spinosa*

<220>

<221> CDS

<222> (1)..(750)

<223> ORF3; O-Methyltransferase

<400> 11

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 Met Pro Ser Gln Asn Ala Leu Tyr Leu Asp Leu Leu Lys Lys Val Leu
 1 5 10 15

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acc aac acg att tac agt gat cgg ccg cat ccg aac gcc tgg cag gac	96
Thr Asn Thr Ile Tyr Ser Asp Arg Pro His Pro Asn Ala Trp Gln Asp	
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aac acc gac tac agg cag gcc gct cgg gcc aaa ggc acg gac tgg cca	144
Asn Thr Asp Tyr Arg Gln Ala Ala Arg Ala Lys Gly Thr Asp Trp Pro	
35 40 45	
act gtc gcg cac acg atg atc ggt ctg gag cgg ctg gac aac ctc cag	192
Thr Val Ala His Thr Met Ile Gly Leu Glu Arg Leu Asp Asn Leu Gln	
50 55 60	
cac tgc gtg gaa gcc gtg ctc gca gac ggt gtt ccc ggg gat ttc gcc	240
His Cys Val Glu Ala Val Leu Ala Asp Gly Val Pro Gly Asp Phe Ala	
65 70 75 80	
gag acc ggt gtc tgg cgg ggc ggc gca tgc atc ttc atg cgc gcg gtt	288
Glu Thr Gly Val Trp Arg Gly Gly Ala Cys Ile Phe Met Arg Ala Val	
85 90 95	
ctc cag gca ttc gga gat acc gga cgt acc gtc tgg gta gtg gat tcc	336
Leu Gln Ala Phe Gly Asp Thr Gly Arg Thr Val Trp Val Val Asp Ser	
100 105 110	
ttc cag gga atg ccg gaa agc tct gcg caa gac cac caa gcg gac cag	384
Phe Gln Gly Met Pro Glu Ser Ser Ala Gln Asp His Gln Ala Asp Gln	
115 120 125	
gct atg gcg ctg cac gag tac aac gac gtg ctt ggc gta tcg ctt gag	432
Ala Met Ala Leu His Glu Tyr Asn Asp Val Leu Gly Val Ser Leu Glu	
130 135 140	
acc gtc cgg cag aac ttc gcc cgc tac ggg ctg ctc gac gaa cag gtc	480
Thr Val Arg Gln Asn Phe Ala Arg Tyr Gly Leu Leu Asp Glu Gln Val	
145 150 155 160	
agg ttc ctc ccc ggc tgg ttc cgg gac acc ttg ccc acc gcc ccc atc	528
Arg Phe Leu Pro Gly Trp Phe Arg Asp Thr Leu Pro Thr Ala Pro Ile	
165 170 175	
cag gaa ctc gcc gtg cta cga ctc gac ggc gac ctc tac gaa tcc aca	576
Gln Glu Leu Ala Val Leu Arg Leu Asp Gly Asp Leu Tyr Glu Ser Thr	
180 185 190	
atg gac tca ttg cgg aac ctg tac ccg aag ctc tcg ccg ggc gga ttc	624
Met Asp Ser Leu Arg Asn Leu Tyr Pro Lys Leu Ser Pro Gly Gly Phe	
195 200 205	

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gtc atc atc gac gac tat ttt ctg ccg tcc tgc cag gac gcg gtg aag 672
 Val Ile Ile Asp Asp Tyr Phe Leu Pro Ser Cys Gln Asp Ala Val Lys
 210 215 220

ggg ttc cgc gcg gaa ctc ggg atc acg gaa ccc atc cac gac atc gac 720
 Gly Phe Arg Ala Glu Leu Gly Ile Thr Glu Pro Ile His Asp Ile Asp
 225 230 235 240

ggc acg ggc gcc tac tgg cgc cgc agc tgg tga 753
 Gly Thr Gly Ala Tyr Trp Arg Arg Ser Trp
 245 250

<210> 12

<211> 250

<212> PRT

<213> Saccharopolyspora spinosa

<400> 12

Met Pro Ser Gln Asn Ala Leu Tyr Leu Asp Leu Leu Lys Lys Val Leu
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Thr Asn Thr Ile Tyr Ser Asp Arg Pro His Pro Asn Ala Trp Gln Asp
 20 25 30

Asn Thr Asp Tyr Arg Gln Ala Ala Arg Ala Lys Gly Thr Asp Trp Pro
 35 40 45

Thr Val Ala His Thr Met Ile Gly Leu Glu Arg Leu Asp Asn Leu Gln
 50 55 60

His Cys Val Glu Ala Val Leu Ala Asp Gly Val Pro Gly Asp Phe Ala
 65 70 75 80

Glu Thr Gly Val Trp Arg Gly Gly Ala Cys Ile Phe Met Arg Ala Val
 85 90 95

Leu Gln Ala Phe Gly Asp Thr Gly Arg Thr Val Trp Val Val Asp Ser
 100 105 110

Phe Gln Gly Met Pro Glu Ser Ser Ala Gln Asp His Gln Ala Asp Gln
 115 120 125

Ala Met Ala Leu His Glu Tyr Asn Asp Val Leu Gly Val Ser Leu Glu
 130 135 140

Thr Val Arg Gln Asn Phe Ala Arg Tyr Gly Leu Leu Asp Glu Gln Val
 145 150 155 160

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Arg Phe Leu Pro Gly Trp Phe Arg Asp Thr Leu Pro Thr Ala Pro Ile
 165 170 175

Gln Glu Leu Ala Val Leu Arg Leu Asp Gly Asp Leu Tyr Glu Ser Thr
 180 185 190

Met Asp Ser Leu Arg Asn Leu Tyr Pro Lys Leu Ser Pro Gly Gly Phe
 195 200 205

Val Ile Ile Asp Asp Tyr Phe Leu Pro Ser Cys Gln Asp Ala Val Lys
 210 215 220

Gly Phe Arg Ala Glu Leu Gly Ile Thr Glu Pro Ile His Asp Ile Asp
 225 230 235 240

Gly Thr Gly Ala Tyr Trp Arg Arg Ser Trp
 245 250

<210> 13

<211> 1188

<212> DNA

<213> Saccharopolyspora spinosa

<220>

<221> CDS

<222> (1) .. (1185)

<223> ORF4; O-Methyltransferase

<400> 13

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 1 5 10 15

ctc gcg gcg ggt gcg ggc ccg gcg aag ctc cag gaa gca gtg cag gtg 96
 Leu Ala Ala Gly Ala Gly Pro Ala Lys Leu Gln Glu Ala Val Gln Val
 20 25 30

gcc gga ctg gac gcg gtg gcc gac gcc atc gtc gac gaa ctc gtc gta 144
 Ala Gly Leu Asp Ala Val Ala Asp Ala Ile Val Asp Glu Leu Val Val
 35 40 45

cgc tgc gat ccg ctg tcg ttg gac gag tcg gtg cga atc ggc ctg gag 192
 Arg Cys Asp Pro Leu Ser Leu Asp Glu Ser Val Arg Ile Gly Leu Glu
 50 55 60

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atc act tct ggc gct cag ctg gtc cgg aga acc gtt gag ctc gat cac	240
Ile Thr Ser Gly Ala Gln Leu Val Arg Arg Thr Val Glu Leu Asp His	
65 70 75 80	
gca ggc ctg cgg ctc gcg gcg gtc gcc gaa gca gct gct gtt ctc cgg	288
Ala Gly Leu Arg Leu Ala Ala Val Ala Glu Ala Ala Ala Val Leu Arg	
85 90 95	
ttc gac gcg gtg gat ctg ctg gaa ggg ctc ttc ggc ccg gtt gac ggc	336
Phe Asp Ala Val Asp Leu Leu Glu Gly Leu Phe Gly Pro Val Asp Gly	
100 105 110	
agg cgg cac aac agc cgt gaa gtc cgc tgg tcg gac agc atg acg cag	384
Arg Arg His Asn Ser Arg Glu Val Arg Trp Ser Asp Ser Met Thr Gln	
115 120 125	
ttc tcg ccc gac cag ggc ctc gcc ggc gcg cag cgc ctg ctg gcg ttc	432
Phe Ser Pro Asp Gln Gly Leu Ala Gly Ala Gln Arg Leu Leu Ala Phe	
130 135 140	
cgg aac agg gtg tcc acc gcg gtg cac gcc gtg ctg gcc gca gcc gcc	480
Arg Asn Arg Val Ser Thr Ala Val His Ala Val Leu Ala Ala Ala Ala	
145 150 155 160	
acc agg cgc gcg gac ctc ggt gcg ctg gca gtc cgc tac gga tcc gac	528
Thr Arg Arg Ala Asp Leu Gly Ala Leu Ala Val Arg Tyr Gly Ser Asp	
165 170 175	
aaa tgg gcg gac ctg cac tgg tac acc gaa cac tac gag cac cac ttc	576
Lys Trp Ala Asp Leu His Trp Tyr Thr Glu His Tyr Glu His His Phe	
180 185 190	
tcc cga ttc cag gat gcc ccg gtg cga gtg ttg gaa ata gga atc ggt	624
Ser Arg Phe Gln Asp Ala Pro Val Arg Val Leu Glu Ile Gly Ile Gly	
195 200 205	
ggt tat cac gca ccc gaa ctc ggt ggt gct tcg ctg cgc atg tgg cag	672
Gly Tyr His Ala Pro Glu Leu Gly Gly Ala Ser Leu Arg Met Trp Gln	
210 215 220	
cgg tac ttc cgg cga ggt ctc gtt tac ggg ctg gac att ttc gag aaa	720
Arg Tyr Phe Arg Arg Gly Leu Val Tyr Gly Leu Asp Ile Phe Glu Lys	
225 230 235 240	
gcc ggg aac gaa ggg cac cga gtg cga aag ctg cga ggt gac cag agc	768
Ala Gly Asn Glu Gly His Arg Val Arg Lys Leu Arg Gly Asp Gln Ser	
245 250 255	

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gat gcg gaa ttc ctg gaa gac atg gcg ggg aag atc ggg ccg ttc gac 816
 Asp Ala Glu Phe Leu Glu Asp Met Ala Gly Lys Ile Gly Pro Phe Asp
 260 265 270

att gtc atc gac gac ggc agc cat gtc aac gac cac gtc aag aaa tcc 864
 Ile Val Ile Asp Asp Gly Ser His Val Asn Asp His Val Lys Lys Ser
 275 280 285

ttc caa tcc ctg ttt ccg cac gtc cgc cca ggt ggt ttg tac gtc atc 912
 Phe Gln Ser Leu Phe Pro His Val Arg Pro Gly Gly Leu Tyr Val Ile
 290 295 300

gag gat ctc cag acg gcg tac tgg ccc ggc tac ggc ggt cgc gat ggg 960
 Glu Asp Leu Gln Thr Ala Tyr Trp Pro Gly Tyr Gly Gly Arg Asp Gly
 305 310 315 320

gaa ccc gcg gcc cag cgc acc tcg atc gac atg ctc aaa gaa ctg atc 1008
 Glu Pro Ala Ala Gln Arg Thr Ser Ile Asp Met Leu Lys Glu Leu Ile
 325 330 335

gac ggc ctg cat tat cag gag cgc gaa tcg cgg tgc ggg acc gag ccc 1056
 Asp Gly Leu His Tyr Gln Glu Arg Glu Ser Arg Cys Gly Thr Glu Pro
 340 345 350

tcc tac acg gaa cgg aac gtg gcg gcc ctg cac ttc tac cac aac ctg 1104
 Ser Tyr Thr Glu Arg Asn Val Ala Ala Leu His Phe Tyr His Asn Leu
 355 360 365

gta ttc gtg gag aaa ggg ctc aac gct gag cct gcc gcg ccg ggg ttc 1152
 Val Phe Val Glu Lys Gly Leu Asn Ala Glu Pro Ala Ala Pro Gly Phe
 370 375 380

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 Val Pro Arg Gln Ala Leu Gly Val Glu Asp Gly
 385 390 395

<210> 14

<211> 395

<212> PRT

<213> Saccharopolyspora spinosa

<400> 14

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Leu Ala Ala Gly Ala Gly Pro Ala Lys Leu Gln Glu Ala Val Gln Val
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Ala Gly Leu Asp Ala Val Ala Asp Ala Ile Val Asp Glu Leu Val Val
 35 40 45

Arg Cys Asp Pro Leu Ser Leu Asp Glu Ser Val Arg Ile Gly Leu Glu
 50 55 60

Ile Thr Ser Gly Ala Gln Leu Val Arg Arg Thr Val Glu Leu Asp His
 65 70 75 80

Ala Gly Leu Arg Leu Ala Ala Val Ala Glu Ala Ala Ala Val Leu Arg
 85 90 95

Phe Asp Ala Val Asp Leu Leu Glu Gly Leu Phe Gly Pro Val Asp Gly
 100 105 110

Arg Arg His Asn Ser Arg Glu Val Arg Trp Ser Asp Ser Met Thr Gln
 115 120 125

Phe Ser Pro Asp Gln Gly Leu Ala Gly Ala Gln Arg Leu Leu Ala Phe
 130 135 140

Arg Asn Arg Val Ser Thr Ala Val His Ala Val Leu Ala Ala Ala Ala
 145 150 155 160

Thr Arg Arg Ala Asp Leu Gly Ala Leu Ala Val Arg Tyr Gly Ser Asp
 165 170 175

Lys Trp Ala Asp Leu His Trp Tyr Thr Glu His Tyr Glu His His Phe
 180 185 190

Ser Arg Phe Gln Asp Ala Pro Val Arg Val Leu Glu Ile Gly Ile Gly
 195 200 205

Gly Tyr His Ala Pro Glu Leu Gly Gly Ala Ser Leu Arg Met Trp Gln
 210 215 220

Arg Tyr Phe Arg Arg Gly Leu Val Tyr Gly Leu Asp Ile Phe Glu Lys
 225 230 235 240

Ala Gly Asn Glu Gly His Arg Val Arg Lys Leu Arg Gly Asp Gln Ser
 245 250 255

Asp Ala Glu Phe Leu Glu Asp Met Ala Gly Lys Ile Gly Pro Phe Asp
 260 265 270

Ile Val Ile Asp Asp Gly Ser His Val Asn Asp His Val Lys Lys Ser
 275 280 285

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Phe Gln Ser Leu Phe Pro His Val Arg Pro Gly Gly Leu Tyr Val Ile
 290 295 300

Glu Asp Leu Gln Thr Ala Tyr Trp Pro Gly Tyr Gly Gly Arg Asp Gly
 305 310 315 320

Glu Pro Ala Ala Gln Arg Thr Ser Ile Asp Met Leu Lys Glu Leu Ile
 325 330 335

Asp Gly Leu His Tyr Gln Glu Arg Glu Ser Arg Cys Gly Thr Glu Pro
 340 345 350

Ser Tyr Thr Glu Arg Asn Val Ala Ala Leu His Phe Tyr His Asn Leu
 355 360 365

Val Phe Val Glu Lys Gly Leu Asn Ala Glu Pro Ala Ala Pro Gly Phe
 370 375 380

Val Pro Arg Gln Ala Leu Gly Val Glu Asp Gly
 385 390 395

<210> 15

<211> 1620

<212> DNA

<213> Saccharopolyspora spinosa

<220>

<221> CDS

<222> (1) .. (1617)

<223> ORF5; C-C verknüpfendes Enzym, Cyclisierungsenzym

<400> 15

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 Met Ile Ser Ala Ala Gly Glu Gln Ser Gly Pro Val Arg Lys Gly Gly
 1 5 10 15

gcg gtg ccc gaa ttc cat gac ccg gca ccc atg aat cgt cga acc cca 96
 Ala Val Pro Glu Phe His Asp Pro Ala Pro Met Asn Arg Arg Thr Pro
 20 25 30

gga aca gag atc acc gtc gag ccc gac gat cct cgt tat ccg gac ctc 144
 Gly Thr Glu Ile Thr Val Glu Pro Asp Asp Pro Arg Tyr Pro Asp Leu
 35 40 45

gtc gtc ggg cac aac ccc cgt ttc acc gga aaa ccc gaa cgc atc cac 192

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Val Val Gly His Asn Pro Arg Phe Thr Gly Lys Pro Glu Arg Ile His	
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atc gcc agc tcc gcc gaa gac gtc gtg cac gcc gtc gcc gac gcc gtg	240
Ile Ala Ser Ser Ala Glu Asp Val Val His Ala Val Ala Asp Ala Val	
65 70 75 80	
cgc acc ggc agg cgg gta ggg gtc cgc agc ggc ggg cac tgc ttc gag	288
Arg Thr Gly Arg Arg Val Gly Val Arg Ser Gly Gly His Cys Phe Glu	
85 90 95	
aat ctc gtt gcg gac ccg gcg atc cga gtg ctc gtc gac ctc tcc gag	336
Asn Leu Val Ala Asp Pro Ala Ile Arg Val Leu Val Asp Leu Ser Glu	
100 105 110	
ctc aac cgc gtg tac tac gac agc acg cgc ggg gca ttc gcg atc gag	384
Leu Asn Arg Val Tyr Tyr Asp Ser Thr Arg Gly Ala Phe Ala Ile Glu	
115 120 125	
gcg ggc gcc gcc ctc ggg cag gtg tac cga acc ctg ttc aag aac tgg	432
Ala Gly Ala Ala Leu Gly Gln Val Tyr Arg Thr Leu Phe Lys Asn Trp	
130 135 140	
ggc gtg acg atc ccg acc ggc gca tgt ccc ggg gtg ggc gca ggc ggg	480
Gly Val Thr Ile Pro Thr Gly Ala Cys Pro Gly Val Gly Ala Gly Gly	
145 150 155 160	
cac atc ctc ggc ggg gga tac ggc ccg ctg tcg cgc cga ttc ggt tcg	528
His Ile Leu Gly Gly Gly Tyr Gly Pro Leu Ser Arg Arg Phe Gly Ser	
165 170 175	
gtc gtc gac tac ctt caa ggc gtc gag gtc gtc gtg gtc gac cag gcc	576
Val Val Asp Tyr Leu Gln Gly Val Glu Val Val Val Val Asp Gln Ala	
180 185 190	
ggg gaa gtg cac atc gtc gag gcc gac cgg aac tcc acg ggc gcc ggt	624
Gly Glu Val His Ile Val Glu Ala Asp Arg Asn Ser Thr Gly Ala Gly	
195 200 205	
cac gac ttg tgg tgg gcg cac acc ggt ggc ggt ggc ggc aac ttc ggg	672
His Asp Leu Trp Trp Ala His Thr Gly Gly Gly Gly Gly Asn Phe Gly	
210 215 220	
atc gtc acc agg ttt tgg ctc cga acg ccg gac gtg gtc agc acc gac	720
Ile Val Thr Arg Phe Trp Leu Arg Thr Pro Asp Val Val Ser Thr Asp	
225 230 235 240	
gcc gca gag ctc ctg cca cgg ccg ccc gcg aca gtg ctg ctc cga tcg	768

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Ala Ala Glu Leu Leu Pro Arg Pro Pro Ala Thr Val Leu Leu Arg Ser	
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ttc cac tgg ccg tgg cac gaa ctg aca gag cag tca ttc gcc gtg ctc	816
Phe His Trp Pro Trp His Glu Leu Thr Glu Gln Ser Phe Ala Val Leu	
260 265 270	
cta cag aac ttc ggc aat tgg tac gag cag cac agc gcg cct gaa tcc	864
Leu Gln Asn Phe Gly Asn Trp Tyr Glu Gln His Ser Ala Pro Glu Ser	
275 280 285	
acg caa ctc ggg ttg ttc agc acg ctc gtc tgc gca cac cgg caa gct	912
Thr Gln Leu Gly Leu Phe Ser Thr Leu Val Cys Ala His Arg Gln Ala	
290 295 300	
ggc tac gtc acg ctg aac gtt cac ctg gac ggc acg gat ccg aac gcg	960
Gly Tyr Val Thr Leu Asn Val His Leu Asp Gly Thr Asp Pro Asn Ala	
305 310 315 320	
gaa cgc acc ctg gcc gaa cac ctg tcg gcg atc aac gcc cag gtc ggc	1008
Glu Arg Thr Leu Ala Glu His Leu Ser Ala Ile Asn Ala Gln Val Gly	
325 330 335	
gtg act cca gcc gaa ggg ctg cgg gaa acc ctg ccg tgg ttg cga tcg	1056
Val Thr Pro Ala Glu Gly Leu Arg Glu Thr Leu Pro Trp Leu Arg Ser	
340 345 350	
acc cag gtg gcc ggg gcg atc gcc gaa ggc ggc gaa ccg ggc atg caa	1104
Thr Gln Val Ala Gly Ala Ile Ala Glu Gly Gly Glu Pro Gly Met Gln	
355 360 365	
cgg acc aag gtc aaa gcc gcc tac ttg cgc acc ggg ctg tcc gaa gct	1152
Arg Thr Lys Val Lys Ala Ala Tyr Leu Arg Thr Gly Leu Ser Glu Ala	
370 375 380	
caa cta gcc acg gtt tac cgg cgg ctg acc gtc tac gga tac gac aac	1200
Gln Leu Ala Thr Val Tyr Arg Arg Leu Thr Val Tyr Gly Tyr Asp Asn	
385 390 395 400	
cct gcg gcg gcg ctg ttg ctg ctc ggt tac ggc ggt atg gcg aat gcc	1248
Pro Ala Ala Ala Leu Leu Leu Leu Gly Tyr Gly Gly Met Ala Asn Ala	
405 410 415	
gtg gct ccg tcg gcc acc gca ctc gct cag cgc gac tcg gtt ctc aaa	1296
Val Ala Pro Ser Ala Thr Ala Leu Ala Gln Arg Asp Ser Val Leu Lys	
420 425 430	
gcg ctg ttc gtc acg aac tgg tcg gag ccc gcc gag gac gag cgg cat	1344

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Ala Leu Phe Val Thr Asn Trp Ser Glu Pro Ala Glu Asp Glu Arg His
 435 440 445

ctg acc tgg att cgc ggt ttc tac cgc gag atg tac gcc gaa acc ggc 1392
 Leu Thr Trp Ile Arg Gly Phe Tyr Arg Glu Met Tyr Ala Glu Thr Gly
 450 455 460

gga gtt ccg gtg cca ggt acc cgt gtc gac ggc tcc tac atc aac tac 1440
 Gly Val Pro Val Pro Gly Thr Arg Val Asp Gly Ser Tyr Ile Asn Tyr
 465 470 475 480

ccg gac acc gac ttg gcc gat cca ttg tgg aac acc tcc ggt gtt gcc 1488
 Pro Asp Thr Asp Leu Ala Asp Pro Leu Trp Asn Thr Ser Gly Val Ala
 485 490 495

tgg cac gac ctg tac tac aaa gac aac tac ccg cgg ctg cag cgg gcc 1536
 Trp His Asp Leu Tyr Tyr Lys Asp Asn Tyr Pro Arg Leu Gln Arg Ala
 500 505 510

aaa gcg cgg tgg gat ccg cag aac atc ttc cag cac ggc ctg tcg atc 1584
 Lys Ala Arg Trp Asp Pro Gln Asn Ile Phe Gln His Gly Leu Ser Ile
 515 520 525

aaa ccg ccg gca cgg ctt tca ccc ggt cag cca tga 1620
 Lys Pro Pro Ala Arg Leu Ser Pro Gly Gln Pro
 530 535

<210> 16
 <211> 539
 <212> PRT
 <213> Saccharopolyspora spinosa

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Ala Val Pro Glu Phe His Asp Pro Ala Pro Met Asn Arg Arg Thr Pro
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Gly Thr Glu Ile Thr Val Glu Pro Asp Asp Pro Arg Tyr Pro Asp Leu
 35 40 45

Val Val Gly His Asn Pro Arg Phe Thr Gly Lys Pro Glu Arg Ile His
 50 55 60

Ile Ala Ser Ser Ala Glu Asp Val Val His Ala Val Ala Asp Ala Val
 65 70 75 80

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Arg Thr Gly Arg Arg Val Gly Val Arg Ser Gly Gly His Cys Phe Glu
 85 90 95
 Asn Leu Val Ala Asp Pro Ala Ile Arg Val Leu Val Asp Leu Ser Glu
 100 105 110
 Leu Asn Arg Val Tyr Tyr Asp Ser Thr Arg Gly Ala Phe Ala Ile Glu
 115 120 125
 Ala Gly Ala Ala Leu Gly Gln Val Tyr Arg Thr Leu Phe Lys Asn Trp
 130 135 140
 Gly Val Thr Ile Pro Thr Gly Ala Cys Pro Gly Val Gly Ala Gly Gly
 145 150 155 160
 His Ile Leu Gly Gly Gly Tyr Gly Pro Leu Ser Arg Arg Phe Gly Ser
 165 170 175
 Val Val Asp Tyr Leu Gln Gly Val Glu Val Val Val Val Asp Gln Ala
 180 185 190
 Gly Glu Val His Ile Val Glu Ala Asp Arg Asn Ser Thr Gly Ala Gly
 195 200 205
 His Asp Leu Trp Trp Ala His Thr Gly Gly Gly Gly Gly Asn Phe Gly
 210 215 220
 Ile Val Thr Arg Phe Trp Leu Arg Thr Pro Asp Val Val Ser Thr Asp
 225 230 235 240
 Ala Ala Glu Leu Leu Pro Arg Pro Pro Ala Thr Val Leu Leu Arg Ser
 245 250 255
 Phe His Trp Pro Trp His Glu Leu Thr Glu Gln Ser Phe Ala Val Leu
 260 265 270
 Leu Gln Asn Phe Gly Asn Trp Tyr Glu Gln His Ser Ala Pro Glu Ser
 275 280 285
 Thr Gln Leu Gly Leu Phe Ser Thr Leu Val Cys Ala His Arg Gln Ala
 290 295 300
 Gly Tyr Val Thr Leu Asn Val His Leu Asp Gly Thr Asp Pro Asn Ala
 305 310 315 320
 Glu Arg Thr Leu Ala Glu His Leu Ser Ala Ile Asn Ala Gln Val Gly
 325 330 335

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Val Thr Pro Ala Glu Gly Leu Arg Glu Thr Leu Pro Trp Leu Arg Ser
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Thr Gln Val Ala Gly Ala Ile Ala Glu Gly Gly Glu Pro Gly Met Gln
 355 360 365

Arg Thr Lys Val Lys Ala Ala Tyr Leu Arg Thr Gly Leu Ser Glu Ala
 370 375 380

Gln Leu Ala Thr Val Tyr Arg Arg Leu Thr Val Tyr Gly Tyr Asp Asn
 385 390 395 400

Pro Ala Ala Ala Leu Leu Leu Gly Tyr Gly Gly Met Ala Asn Ala
 405 410 415

Val Ala Pro Ser Ala Thr Ala Leu Ala Gln Arg Asp Ser Val Leu Lys
 420 425 430

Ala Leu Phe Val Thr Asn Trp Ser Glu Pro Ala Glu Asp Glu Arg His
 435 440 445

Leu Thr Trp Ile Arg Gly Phe Tyr Arg Glu Met Tyr Ala Glu Thr Gly
 450 455 460

Gly Val Pro Val Pro Gly Thr Arg Val Asp Gly Ser Tyr Ile Asn Tyr
 465 470 475 480

Pro Asp Thr Asp Leu Ala Asp Pro Leu Trp Asn Thr Ser Gly Val Ala
 485 490 495

Trp His Asp Leu Tyr Tyr Lys Asp Asn Tyr Pro Arg Leu Gln Arg Ala
 500 505 510

Lys Ala Arg Trp Asp Pro Gln Asn Ile Phe Gln His Gly Leu Ser Ile
 515 520 525

Lys Pro Pro Ala Arg Leu Ser Pro Gly Gln Pro
 530 535

<210> 17

<211> 1194

<212> DNA

<213> Saccharopolyspora spinosa

<220>

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<221> CDS

<222> (1)..(1191)

<223> ORF6; Methyltransferase

<400> 17

atg tcc aca acg cac gag atc gaa acc gtg gaa cgc atc atc ctc gcc	48
Met Ser Thr Thr His Glu Ile Glu Thr Val Glu Arg Ile Ile Leu Ala	
1 5 10 15	

gcc gga tcc agt gcg gcg agc ctg gcc gac ctg acc acc gaa ctc gga	96
Ala Gly Ser Ser Ala Ala Ser Leu Ala Asp Leu Thr Thr Glu Leu Gly	
20 25 30	

ctc gcc agg atc gca ccc gtg ctg atc gac gag atc ctc ttc cgc gcg	144
Leu Ala Arg Ile Ala Pro Val Leu Ile Asp Glu Ile Leu Phe Arg Ala	
35 40 45	

gaa ccg gcc ccc gac atc gaa cgg acc gag gtc gcg gtc cag atc acc	192
Glu Pro Ala Pro Asp Ile Glu Arg Thr Glu Val Ala Val Gln Ile Thr	
50 55 60	

cac cga ggc gag acc gtt gac ttc gtc ctg acg cta cag tcc ggt gag	240
His Arg Gly Glu Thr Val Asp Phe Val Leu Thr Leu Gln Ser Gly Glu	
65 70 75 80	

ctg atc aag gcc gag caa cga ccg gtc gga gac gtc ccg ctg cgg atc	288
Leu Ile Lys Ala Glu Gln Arg Pro Val Gly Asp Val Pro Leu Arg Ile	
85 90 95	

ggt tac gag ctc acc gat ctc atc gcc gag ttg ttc ggc cca gga gct	336
Gly Tyr Glu Leu Thr Asp Leu Ile Ala Glu Leu Phe Gly Pro Gly Ala	
100 105 110	

ccc agg gcc gtc ggc gcc cgg agc acc aac ttc ctc cga acc acc aca	384
Pro Arg Ala Val Gly Ala Arg Ser Thr Asn Phe Leu Arg Thr Thr Thr	
115 120 125	

tcc ggt tcg ata ccc ggt ccg tcg gaa ctg tcc gat ggc ttc cag gcc	432
Ser Gly Ser Ile Pro Gly Pro Ser Glu Leu Ser Asp Gly Phe Gln Ala	
130 135 140	

atc tcc gca gtg gtc gcc ggc tgc ggg cac cga cgt ccc gac ctc aac	480
Ile Ser Ala Val Val Ala Gly Cys Gly His Arg Arg Pro Asp Leu Asn	
145 150 155 160	

ttg ctc gcc tcc cac tac cgc acg gac aag tgg ggc ggc ctg cac tgg	528
Leu Leu Ala Ser His Tyr Arg Thr Asp Lys Trp Gly Gly Leu His Trp	
165 170 175	

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ttc acc ccg cta tac gag cga cac ctc ggc gag ttc cgt gat cgc ccg	576
Phe Thr Pro Leu Tyr Glu Arg His Leu Gly Glu Phe Arg Asp Arg Pro	
180 185 190	
gtg cgc atc ctg gag atc ggt gtc ggt ggc tac aac ttc gac ggt ggc	624
Val Arg Ile Leu Glu Ile Gly Val Gly Gly Tyr Asn Phe Asp Gly Gly	
195 200 205	
ggc ggc gaa tcc ctg aag atg tgg aag cgc tac ttc cac cgc ggc ctc	672
Gly Gly Glu Ser Leu Lys Met Trp Lys Arg Tyr Phe His Arg Gly Leu	
210 215 220	
gtg ttc ggg atg gac gtt ttc gac aag tcc ttc ctc gac cag cag agg	720
Val Phe Gly Met Asp Val Phe Asp Lys Ser Phe Leu Asp Gln Gln Arg	
225 230 235 240	
ctc tgc acc gtc cgc gcc gac cag agc aag ccc gag gag ctg gcc gcc	768
Leu Cys Thr Val Arg Ala Asp Gln Ser Lys Pro Glu Glu Leu Ala Ala	
245 250 255	
gtt gac gac aag tac gga ccg ttc gac atc atc atc gac gat ggc agc	816
Val Asp Asp Lys Tyr Gly Pro Phe Asp Ile Ile Ile Asp Asp Gly Ser	
260 265 270	
cac atc aac gga cac gtg cgc aca tcc ctg gaa acg ctg ttc ccc ccg	864
His Ile Asn Gly His Val Arg Thr Ser Leu Glu Thr Leu Phe Pro Arg	
275 280 285	
ttg cgc agc ggt ggc gta tac gtg atc gag gat ctg tgg acg acc tat	912
Leu Arg Ser Gly Gly Val Tyr Val Ile Glu Asp Leu Trp Thr Thr Tyr	
290 295 300	
gct ccc gga ttc ggc ggg cag gcg cag tgc ccg gcc gca ccc ggc acc	960
Ala Pro Gly Phe Gly Gly Gln Ala Gln Cys Pro Ala Ala Pro Gly Thr	
305 310 315 320	
acg gtc agc ctg ctc aag aac ctg ttg gaa ggc gtt cag cac gag gag	1008
Thr Val Ser Leu Leu Lys Asn Leu Leu Glu Gly Val Gln His Glu Glu	
325 330 335	
cag ccg cat gcg ggc tcg tac gag ccg agc tac ctg gaa cgc aat ttg	1056
Gln Pro His Ala Gly Ser Tyr Glu Pro Ser Tyr Leu Glu Arg Asn Leu	
340 345 350	
gtc ggc ctc cac acc tac cac aac atc gcg ttc ctg gag aaa ggc gtc	1104
Val Gly Leu His Thr Tyr His Asn Ile Ala Phe Leu Glu Lys Gly Val	
355 360 365	

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aac gcc gaa ggc ggc gtt cct gct tgg gtg cca agg agt ctg gac gac 1152
 Asn Ala Glu Gly Gly Val Pro Ala Trp Val Pro Arg Ser Leu Asp Asp
 370 375 380

ata ttg cac ctg gcc gac gtg aac agc gcg gag gac gag tga 1194
 Ile Leu His Leu Ala Asp Val Asn Ser Ala Glu Asp Glu
 385 390 395

<210> 18

<211> 397

<212> PRT

<213> Saccharopolyspora spinosa

<400> 18

Met Ser Thr Thr His Glu Ile Glu Thr Val Glu Arg Ile Ile Leu Ala
 1 5 10 15

Ala Gly Ser Ser Ala Ala Ser Leu Ala Asp Leu Thr Thr Glu Leu Gly
 20 25 30

Leu Ala Arg Ile Ala Pro Val Leu Ile Asp Glu Ile Leu Phe Arg Ala
 35 40 45

Glu Pro Ala Pro Asp Ile Glu Arg Thr Glu Val Ala Val Gln Ile Thr
 50 55 60

His Arg Gly Glu Thr Val Asp Phe Val Leu Thr Leu Gln Ser Gly Glu
 65 70 75 80

Leu Ile Lys Ala Glu Gln Arg Pro Val Gly Asp Val Pro Leu Arg Ile
 85 90 95

Gly Tyr Glu Leu Thr Asp Leu Ile Ala Glu Leu Phe Gly Pro Gly Ala
 100 105 110

Pro Arg Ala Val Gly Ala Arg Ser Thr Asn Phe Leu Arg Thr Thr Thr
 115 120 125

Ser Gly Ser Ile Pro Gly Pro Ser Glu Leu Ser Asp Gly Phe Gln Ala
 130 135 140

Ile Ser Ala Val Val Ala Gly Cys Gly His Arg Arg Pro Asp Leu Asn
 145 150 155 160

Leu Leu Ala Ser His Tyr Arg Thr Asp Lys Trp Gly Gly Leu His Trp
 165 170 175

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Phe Thr Pro Leu Tyr Glu Arg His Leu Gly Glu Phe Arg Asp Arg Pro
 180 185 190
 Val Arg Ile Leu Glu Ile Gly Val Gly Gly Tyr Asn Phe Asp Gly Gly
 195 200 205
 Gly Gly Glu Ser Leu Lys Met Trp Lys Arg Tyr Phe His Arg Gly Leu
 210 215 220
 Val Phe Gly Met Asp Val Phe Asp Lys Ser Phe Leu Asp Gln Gln Arg
 225 230 235 240
 Leu Cys Thr Val Arg Ala Asp Gln Ser Lys Pro Glu Glu Leu Ala Ala
 245 250 255
 Val Asp Asp Lys Tyr Gly Pro Phe Asp Ile Ile Ile Asp Asp Gly Ser
 260 265 270
 His Ile Asn Gly His Val Arg Thr Ser Leu Glu Thr Leu Phe Pro Arg
 275 280 285
 Leu Arg Ser Gly Gly Val Tyr Val Ile Glu Asp Leu Trp Thr Thr Tyr
 290 295 300
 Ala Pro Gly Phe Gly Gly Gln Ala Gln Cys Pro Ala Ala Pro Gly Thr
 305 310 315 320
 Thr Val Ser Leu Leu Lys Asn Leu Leu Glu Gly Val Gln His Glu Glu
 325 330 335
 Gln Pro His Ala Gly Ser Tyr Glu Pro Ser Tyr Leu Glu Arg Asn Leu
 340 345 350
 Val Gly Leu His Thr Tyr His Asn Ile Ala Phe Leu Glu Lys Gly Val
 355 360 365
 Asn Ala Glu Gly Gly Val Pro Ala Trp Val Pro Arg Ser Leu Asp Asp
 370 375 380
 Ile Leu His Leu Ala Asp Val Asn Ser Ala Glu Asp Glu
 385 390 395

<210> 19

<211> 900

<212> DNA

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<213> Saccharopolyspora spinosa

<220>

<221> CDS

<222> (1)..(897)

<223> ORF7; O-Methyltransferase

<400> 19

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 Val Asn Ser Arg Gly Ala Asn Thr Gln Ala Phe Pro Thr Ala Asp Gln
 1 5 10 15

gtg gag tcc atc ttc gat gcg ttg gcg cac ggg cgt ccc ctg cac cac 96
 Val Glu Ser Ile Phe Asp Ala Leu Ala His Gly Arg Pro Leu His His
 20 25 30

ggt tac tgg gcg ggc ggg tat cgg gag gat gcc ggt gcc aca ccg tgg 144
 Gly Tyr Trp Ala Gly Gly Tyr Arg Glu Asp Ala Gly Ala Thr Pro Trp
 35 40 45

tcg gat gct gcc gac caa ctg acc gac ctg ttc atc gac aag gcc gcg 192
 Ser Asp Ala Ala Asp Gln Leu Thr Asp Leu Phe Ile Asp Lys Ala Ala
 50 55 60

ctc cgt ccc gga gcg cac ctg ttc gac ctg ggc tgc ggc aat ggg cag 240
 Leu Arg Pro Gly Ala His Leu Phe Asp Leu Gly Cys Gly Asn Gly Gln
 65 70 75 80

ccc gta gtc cgt gcg gca tgc gcc agc ggc gtt cga gtc acc gga atc 288
 Pro Val Val Arg Ala Ala Cys Ala Ser Gly Val Arg Val Thr Gly Ile
 85 90 95

acc gtg aac gcc cag cat ctc gcc gcc gcc acc agg ctc gcc aac gag 336
 Thr Val Asn Ala Gln His Leu Ala Ala Ala Thr Arg Leu Ala Asn Glu
 100 105 110

acc gga ctg gcc ggc agt ctt gag ttc gat cta gtc gac ggc gcc cag 384
 Thr Gly Leu Ala Gly Ser Leu Glu Phe Asp Leu Val Asp Gly Ala Gln
 115 120 125

ctg ccc tac ccg gac ggt ttc ttt cag gcc gca tgg gcg atg cag tcc 432
 Leu Pro Tyr Pro Asp Gly Phe Phe Gln Ala Ala Trp Ala Met Gln Ser
 130 135 140

gtc gtg cag atc gtg gac cag gcc gcc gcg atc cgc gag gtc cac cga 480
 Val Val Gln Ile Val Asp Gln Ala Ala Ala Ile Arg Glu Val His Arg
 145 150 155 160

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atc ctg gaa ccc ggc ggc cgg ttc gtc ctc gga gac atc atc act cgg 528
 Ile Leu Glu Pro Gly Gly Arg Phe Val Leu Gly Asp Ile Ile Thr Arg
 165 170 175

gtt cga ctc ccg gaa gag tac gcg gcg gtt tgg acg ggc acg acc gcc 576
 Val Arg Leu Pro Glu Glu Tyr Ala Ala Val Trp Thr Gly Thr Thr Ala
 180 185 190

cat acc ttg aac agc ttc acg gcg ctg gtc agc gaa gcc ggg ttc gag 624
 His Thr Leu Asn Ser Phe Thr Ala Leu Val Ser Glu Ala Gly Phe Glu
 195 200 205

att ctc gaa gtc acc gac ctc acg gca cag acc agg tgc atg gtc tcc 672
 Ile Leu Glu Val Thr Asp Leu Thr Ala Gln Thr Arg Cys Met Val Ser
 210 215 220

tgg tac gtc gac gag ttg ctc cgg aaa ctc gat gag ctc gcc ggc gtc 720
 Trp Tyr Val Asp Glu Leu Leu Arg Lys Leu Asp Glu Leu Ala Gly Val
 225 230 235 240

gag cct gcg gct gtc ggc acc tac cag caa cgc tac ttg gga gac atc 768
 Glu Pro Ala Ala Val Gly Thr Tyr Gln Gln Arg Tyr Leu Gly Asp Ile
 245 250 255

gcg gcg aag cac gga ccg gga cca gca cag ctg atc gcc gcg gtt gcg 816
 Ala Ala Lys His Gly Pro Gly Pro Ala Gln Leu Ile Ala Ala Val Ala
 260 265 270

gaa tac cgg aaa cat ccg gat tac gcc aga aac gag gaa agc atg ggt 864
 Glu Tyr Arg Lys His Pro Asp Tyr Ala Arg Asn Glu Glu Ser Met Gly
 275 280 285

ttc atg ctc ctg cag gct cga aag aag cag tcc tga 900
 Phe Met Leu Leu Gln Ala Arg Lys Lys Gln Ser
 290 295

<210> 20

<211> 299

<212> PRT

<213> Saccharopolyspora spinosa

<400> 20

Val Asn Ser Arg Gly Ala Asn Thr Gln Ala Phe Pro Thr Ala Asp Gln
 1 5 10 15

Val Glu Ser Ile Phe Asp Ala Leu Ala His Gly Arg Pro Leu His His
 20 25 30

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Gly Tyr Trp Ala Gly Gly Tyr Arg Glu Asp Ala Gly Ala Thr Pro Trp
 35 40 45

Ser Asp Ala Ala Asp Gln Leu Thr Asp Leu Phe Ile Asp Lys Ala Ala
 50 55 60

Leu Arg Pro Gly Ala His Leu Phe Asp Leu Gly Cys Gly Asn Gly Gln
 65 70 75 80

Pro Val Val Arg Ala Ala Cys Ala Ser Gly Val Arg Val Thr Gly Ile
 85 90 95

Thr Val Asn Ala Gln His Leu Ala Ala Ala Thr Arg Leu Ala Asn Glu
 100 105 110

Thr Gly Leu Ala Gly Ser Leu Glu Phe Asp Leu Val Asp Gly Ala Gln
 115 120 125

Leu Pro Tyr Pro Asp Gly Phe Phe Gln Ala Ala Trp Ala Met Gln Ser
 130 135 140

Val Val Gln Ile Val Asp Gln Ala Ala Ala Ile Arg Glu Val His Arg
 145 150 155 160

Ile Leu Glu Pro Gly Gly Arg Phe Val Leu Gly Asp Ile Ile Thr Arg
 165 170 175

Val Arg Leu Pro Glu Glu Tyr Ala Ala Val Trp Thr Gly Thr Thr Ala
 180 185 190

His Thr Leu Asn Ser Phe Thr Ala Leu Val Ser Glu Ala Gly Phe Glu
 195 200 205

Ile Leu Glu Val Thr Asp Leu Thr Ala Gln Thr Arg Cys Met Val Ser
 210 215 220

Trp Tyr Val Asp Glu Leu Leu Arg Lys Leu Asp Glu Leu Ala Gly Val
 225 230 235 240

Glu Pro Ala Ala Val Gly Thr Tyr Gln Gln Arg Tyr Leu Gly Asp Ile
 245 250 255

Ala Ala Lys His Gly Pro Gly Pro Ala Gln Leu Ile Ala Ala Val Ala
 260 265 270

Glu Tyr Arg Lys His Pro Asp Tyr Ala Arg Asn Glu Glu Ser Met Gly
 275 280 285

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Phe Met Leu Leu Gln Ala Arg Lys Lys Gln Ser
290 295

<210> 21

<211> 1167

<212> DNA

<213> Saccharopolyspora spinosa

<220>

<221> CDS

<222> (1)..(1164)

<223> ORF8; Cyclisierungsenzym

<400> 21

atg gcc tcc gag cac gcc agc ctg gtc ggc gac gat ctg cgg gca ccc 48
Met Ala Ser Glu His Ala Ser Leu Val Gly Asp Asp Leu Arg Ala Pro
1 5 10 15

gcg gat gat ccc ttc tac cga ccg ccg acg ccg cta ccg ccg ggt gtc 96
Ala Asp Asp Pro Phe Tyr Arg Pro Pro Thr Pro Leu Pro Pro Gly Val
20 25 30

ccg ggc acg ctc ctc agg gcc ccg ccc gtc tcg gca ctg cgc ggc acg 144
Pro Gly Thr Leu Leu Arg Ala Arg Pro Val Ser Ala Leu Arg Gly Thr
35 40 45

ggc gaa ccc gtc gca gcc aag gcc tgg caa atc ctc tac cgg tcc aac 192
Gly Glu Pro Val Ala Ala Lys Ala Trp Gln Ile Leu Tyr Arg Ser Asn
50 55 60

tcc gcc ctt ggc atg ccg aac gcc gtc tcc ggc acc gtt ctg gtg ccg 240
Ser Ala Leu Gly Met Pro Asn Ala Val Ser Gly Thr Val Leu Val Pro
65 70 75 80

aac atc ccg tgg ccg cgc gaa gat cgc ccc atc atc act ttc gca gtg 288
Asn Ile Pro Trp Pro Arg Glu Asp Arg Pro Ile Ile Thr Phe Ala Val
85 90 95

ggc acc cac ggc ctc ggt agc caa gtt gcc ccg tcg tac ctg ctt cga 336
Gly Thr His Gly Leu Gly Ser Gln Val Ala Pro Ser Tyr Leu Leu Arg
100 105 110

acc gga acc gag ccg gag acc gag ctg atc gcc gtg gcc ctc gac cgc 384
Thr Gly Thr Glu Pro Glu Thr Glu Leu Ile Ala Val Ala Leu Asp Arg
115 120 125

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ggg tgg gcc gtg gtc atc acc gac tac gaa ggc ctc ggt act cct gga	432
Gly Trp Ala Val Val Ile Thr Asp Tyr Glu Gly Leu Gly Thr Pro Gly	
130 135 140	
acc cac acc tac acc gtc ggc agg gcg cag gga cac gcc atg ctc gat	480
Thr His Thr Tyr Thr Val Gly Arg Ala Gln Gly His Ala Met Leu Asp	
145 150 155 160	
gcc gcc cgc gct gcg caa cgg cta ccg ggc tcc ggc ctg acg acc gac	528
Ala Ala Arg Ala Ala Gln Arg Leu Pro Gly Ser Gly Leu Thr Thr Asp	
165 170 175	
tgc ccg gtc ggc atc tgg ggc tat gcg cag ggt ggg caa gcg tcg gcc	576
Cys Pro Val Gly Ile Trp Gly Tyr Ala Gln Gly Gly Gln Ala Ser Ala	
180 185 190	
ttc gcc ggc gaa ctg cac ccc acc tac gca cct gaa ctg cga atc cgc	624
Phe Ala Gly Glu Leu His Pro Thr Tyr Ala Pro Glu Leu Arg Ile Arg	
195 200 205	
gct gcg gcc gca ggt gcg gtg ccg atc gat ctg ctg gac atc atc cac	672
Ala Ala Ala Ala Gly Ala Val Pro Ile Asp Leu Leu Asp Ile Ile His	
210 215 220	
cga aat gac ggg gtg ttc acc ggg ccg gtg ctg gcc ggc ctg gtc ggg	720
Arg Asn Asp Gly Val Phe Thr Gly Pro Val Leu Ala Gly Leu Val Gly	
225 230 235 240	
cat gcc gct gcc tac ccc gat ctg cca ttc gac gag ctt ctc acc gaa	768
His Ala Ala Ala Tyr Pro Asp Leu Pro Phe Asp Glu Leu Leu Thr Glu	
245 250 255	
gcg ggt cgt acc gcc gtt gat caa gtg cgc gag ctc ggt gca ccg gag	816
Ala Gly Arg Thr Ala Val Asp Gln Val Arg Glu Leu Gly Ala Pro Glu	
260 265 270	
ctc gtc acc cgc ttc ctc ggc cgc gag ctg agc gac ttc ctc gac act	864
Leu Val Thr Arg Phe Leu Gly Arg Glu Leu Ser Asp Phe Leu Asp Thr	
275 280 285	
tcc ggc ctt ttc gag caa cct cga tgg cgc gca cga ctg gcc gaa agc	912
Ser Gly Leu Phe Glu Gln Pro Arg Trp Arg Ala Arg Leu Ala Glu Ser	
290 295 300	
gtc gca ggt agg aac ggt ggc ccg gtg gtc ccc acg ctc gtc tac cac	960
Val Ala Gly Arg Asn Gly Gly Pro Val Val Pro Thr Leu Val Tyr His	
305 310 315 320	

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agc acg gac gac gag atc gtt ccg ttc gca ttc ggc gag cga ctc cgg 1008
 Ser Thr Asp Asp Glu Ile Val Pro Phe Ala Phe Gly Glu Arg Leu Arg
 325 330 335

gac agc tac cgc gcg gcg ggt acg cca gtg cgg tgg cat ccg ctc tcc 1056
 Asp Ser Tyr Arg Ala Ala Gly Thr Pro Val Arg Trp His Pro Leu Ser
 340 345 350

gga ttg gct cac ttt ccc gcc gcc ctg gcc agc tcg cga gtg gtc gtc 1104
 Gly Leu Ala His Phe Pro Ala Ala Leu Ala Ser Ser Arg Val Val Val
 355 360 365

tcg tgg ttc gac gag cac ttc tcc gag ccg tcc gcg atc agc ggt ccg 1152
 Ser Trp Phe Asp Glu His Phe Ser Glu Pro Ser Ala Ile Ser Gly Pro
 370 375 380

cga gat gcc agg tga 1167
 Arg Asp Ala Arg
 385

<210> 22

<211> 388

<212> PRT

<213> Saccharopolyspora spinosa

<400> 22

Met Ala Ser Glu His Ala Ser Leu Val Gly Asp Asp Leu Arg Ala Pro
 1 5 10 15

Ala Asp Asp Pro Phe Tyr Arg Pro Pro Thr Pro Leu Pro Pro Gly Val
 20 25 30

Pro Gly Thr Leu Leu Arg Ala Arg Pro Val Ser Ala Leu Arg Gly Thr
 35 40 45

Gly Glu Pro Val Ala Ala Lys Ala Trp Gln Ile Leu Tyr Arg Ser Asn
 50 55 60

Ser Ala Leu Gly Met Pro Asn Ala Val Ser Gly Thr Val Leu Val Pro
 65 70 75 80

Asn Ile Pro Trp Pro Arg Glu Asp Arg Pro Ile Ile Thr Phe Ala Val
 85 90 95

Gly Thr His Gly Leu Gly Ser Gln Val Ala Pro Ser Tyr Leu Leu Arg
 100 105 110

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Thr Gly Thr Glu Pro Glu Thr Glu Leu Ile Ala Val Ala Leu Asp Arg
 115 120 125

Gly Trp Ala Val Val Ile Thr Asp Tyr Glu Gly Leu Gly Thr Pro Gly
 130 135 140

Thr His Thr Tyr Thr Val Gly Arg Ala Gln Gly His Ala Met Leu Asp
 145 150 155 160

Ala Ala Arg Ala Ala Gln Arg Leu Pro Gly Ser Gly Leu Thr Thr Asp
 165 170 175

Cys Pro Val Gly Ile Trp Gly Tyr Ala Gln Gly Gly Gln Ala Ser Ala
 180 185 190

Phe Ala Gly Glu Leu His Pro Thr Tyr Ala Pro Glu Leu Arg Ile Arg
 195 200 205

Ala Ala Ala Ala Gly Ala Val Pro Ile Asp Leu Leu Asp Ile Ile His
 210 215 220

Arg Asn Asp Gly Val Phe Thr Gly Pro Val Leu Ala Gly Leu Val Gly
 225 230 235 240

His Ala Ala Ala Tyr Pro Asp Leu Pro Phe Asp Glu Leu Leu Thr Glu
 245 250 255

Ala Gly Arg Thr Ala Val Asp Gln Val Arg Glu Leu Gly Ala Pro Glu
 260 265 270

Leu Val Thr Arg Phe Leu Gly Arg Glu Leu Ser Asp Phe Leu Asp Thr
 275 280 285

Ser Gly Leu Phe Glu Gln Pro Arg Trp Arg Ala Arg Leu Ala Glu Ser
 290 295 300

Val Ala Gly Arg Asn Gly Gly Pro Val Val Pro Thr Leu Val Tyr His
 305 310 315 320

Ser Thr Asp Asp Glu Ile Val Pro Phe Ala Phe Gly Glu Arg Leu Arg
 325 330 335

Asp Ser Tyr Arg Ala Ala Gly Thr Pro Val Arg Trp His Pro Leu Ser
 340 345 350

Gly Leu Ala His Phe Pro Ala Ala Leu Ala Ser Ser Arg Val Val Val
 355 360 365

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Ser Trp Phe Asp Glu His Phe Ser Glu Pro Ser Ala Ile Ser Gly Pro
 370 375 380

Arg Asp Ala Arg
 385

<210> 23

<211> 1011

<212> DNA

<213> Saccharopolyspora spinosa

<220>

<221> CDS

<222> (1)..(1008)

<223> ORF9; 2,3-Reduktase

<400> 23

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 Met Thr Ser Ser Met Arg Lys Pro Val Arg Ile Gly Val Leu Gly Cys
 1 5 10 15

gct tcc ttc gcg tgg cga cgg atg ctg ccc gcg atg tgc gac gtg gcc 96
 Ala Ser Phe Ala Trp Arg Arg Met Leu Pro Ala Met Cys Asp Val Ala
 20 25 30

gaa aca gag gtg gtg gcg gtg gcg agc cgt gat ccg gcg aaa gcc gaa 144
 Glu Thr Glu Val Val Ala Val Ala Ser Arg Asp Pro Ala Lys Ala Glu
 35 40 45

cgg ttc gca gcg cga ttc gaa tgc gag gcg gtg ctg ggt tac cag cgg 192
 Arg Phe Ala Ala Arg Phe Glu Cys Glu Ala Val Leu Gly Tyr Gln Arg
 50 55 60

ctc ctg gag cgg ccg gac atc gat gcc gtc tac gtg ccg ttg ccg cct 240
 Leu Leu Glu Arg Pro Asp Ile Asp Ala Val Tyr Val Pro Leu Pro Pro
 65 70 75 80

ggc atg cat gca gag tgg atc ggc aag gcg ctt gag gca gac aaa cac 288
 Gly Met His Ala Glu Trp Ile Gly Lys Ala Leu Glu Ala Asp Lys His
 85 90 95

gtg ctt gcg gag aaa ccg ctg acg acg acg gcg tcc gac acc gct cgc 336
 Val Leu Ala Glu Lys Pro Leu Thr Thr Thr Ala Ser Asp Thr Ala Arg
 100 105 110

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ctg gtc ggg ctg gcc agg agg aag aac ctg ctg ctg cgg gag aat tac	384
Leu Val Gly Leu Ala Arg Arg Lys Asn Leu Leu Leu Arg Glu Asn Tyr	
115 120 125	
ctg ttc ctc cac cac ggc cgg cac gac gtg gtc cgc gac ctg ctg caa	432
Leu Phe Leu His His Gly Arg His Asp Val Val Arg Asp Leu Leu Gln	
130 135 140	
tcc ggg gag atc ggt gag ctc cgg gag ttc acc gcc gtg ttc gga att	480
Ser Gly Glu Ile Gly Glu Leu Arg Glu Phe Thr Ala Val Phe Gly Ile	
145 150 155 160	
ccg ccg ctt ccc gac acg gac atc cgc tat cgc acc gaa ctc ggt ggc	528
Pro Pro Leu Pro Asp Thr Asp Ile Arg Tyr Arg Thr Glu Leu Gly Gly	
165 170 175	
gga gcg ttg ctg gac atc ggt gtc tat ccc gcc cgt gcc gct cgg cac	576
Gly Ala Leu Leu Asp Ile Gly Val Tyr Pro Ala Arg Ala Ala Arg His	
180 185 190	
ttt ctc ctc ggt ccg ctc acg gtt ctc ggc gca agc tcg cac gag gcc	624
Phe Leu Leu Gly Pro Leu Thr Val Leu Gly Ala Ser Ser His Glu Ala	
195 200 205	
cag gag tcg ggc gtc gac ttg tcg ggc agc gtg ctg ctc caa tcg gaa	672
Gln Glu Ser Gly Val Asp Leu Ser Gly Ser Val Leu Leu Gln Ser Glu	
210 215 220	
ggt ggc acc gtt gcc cac ctc gga tac ggt ttc gtg cac cac tac cgc	720
Gly Gly Thr Val Ala His Leu Gly Tyr Gly Phe Val His His Tyr Arg	
225 230 235 240	
agc gcg tac gag ctg tgg ggg agt cgt ggg cga atc gtc gtc gac cgg	768
Ser Ala Tyr Glu Leu Trp Gly Ser Arg Gly Arg Ile Val Val Asp Arg	
245 250 255	
gcg ttc acg ccg ccc gcc gag tgg cag gcc gtg atc cga atc gag cgg	816
Ala Phe Thr Pro Pro Ala Glu Trp Gln Ala Val Ile Arg Ile Glu Arg	
260 265 270	
aag ggc gtt gtc gac gag ttg tcc ttg cca gcg gaa gat cag gtt cgc	864
Lys Gly Val Val Asp Glu Leu Ser Leu Pro Ala Glu Asp Gln Val Arg	
275 280 285	
aag gcg gtc acc gcc ttc gca cgc gac atc aga gca ggg aca ggc gtg	912
Lys Ala Val Thr Ala Phe Ala Arg Asp Ile Arg Ala Gly Thr Gly Val	
290 295 300	

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gac gac cct gcg gtg gcc gga gat tcg ggc gaa tcg atg atc cag cag 960
 Asp Asp Pro Ala Val Ala Gly Asp Ser Gly Glu Ser Met Ile Gln Gln
 305 310 315 320

 gcc gcg ctg gtg gag gcg atc ggt cag gcc cgt cgg tgc ggg tcc aca 1008
 Ala Ala Leu Val Glu Ala Ile Gly Gln Ala Arg Arg Cys Gly Ser Thr
 325 330 335

 tag 1011

<210> 24

<211> 336

<212> PRT

<213> *Saccharopolyspora spinosa*

<400> 24

Met Thr Ser Ser Met Arg Lys Pro Val Arg Ile Gly Val Leu Gly Cys
 1 5 10 15

Ala Ser Phe Ala Trp Arg Arg Met Leu Pro Ala Met Cys Asp Val Ala
 20 25 30

Glu Thr Glu Val Val Ala Val Ala Ser Arg Asp Pro Ala Lys Ala Glu
 35 40 45

Arg Phe Ala Ala Arg Phe Glu Cys Glu Ala Val Leu Gly Tyr Gln Arg
 50 55 60

Leu Leu Glu Arg Pro Asp Ile Asp Ala Val Tyr Val Pro Leu Pro Pro
 65 70 75 80

Gly Met His Ala Glu Trp Ile Gly Lys Ala Leu Glu Ala Asp Lys His
 85 90 95

Val Leu Ala Glu Lys Pro Leu Thr Thr Thr Ala Ser Asp Thr Ala Arg
 100 105 110

Leu Val Gly Leu Ala Arg Arg Lys Asn Leu Leu Leu Arg Glu Asn Tyr
 115 120 125

Leu Phe Leu His His Gly Arg His Asp Val Val Arg Asp Leu Leu Gln
 130 135 140

Ser Gly Glu Ile Gly Glu Leu Arg Glu Phe Thr Ala Val Phe Gly Ile
 145 150 155 160

Pro Pro Leu Pro Asp Thr Asp Ile Arg Tyr Arg Thr Glu Leu Gly Gly

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	165		170		175
Gly Ala Leu Leu Asp Ile Gly Val Tyr Pro Ala Arg Ala Ala Arg His					
	180		185		190
Phe Leu Leu Gly Pro Leu Thr Val Leu Gly Ala Ser Ser His Glu Ala					
	195		200		205
Gln Glu Ser Gly Val Asp Leu Ser Gly Ser Val Leu Leu Gln Ser Glu					
	210		215		220
Gly Gly Thr Val Ala His Leu Gly Tyr Gly Phe Val His His Tyr Arg					
	225		230		235
					240
Ser Ala Tyr Glu Leu Trp Gly Ser Arg Gly Arg Ile Val Val Asp Arg					
	245		250		255
Ala Phe Thr Pro Pro Ala Glu Trp Gln Ala Val Ile Arg Ile Glu Arg					
	260		265		270
Lys Gly Val Val Asp Glu Leu Ser Leu Pro Ala Glu Asp Gln Val Arg					
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Lys Ala Val Thr Ala Phe Ala Arg Asp Ile Arg Ala Gly Thr Gly Val					
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Asp Asp Pro Ala Val Ala Gly Asp Ser Gly Glu Ser Met Ile Gln Gln					
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					320
Ala Ala Leu Val Glu Ala Ile Gly Gln Ala Arg Arg Cys Gly Ser Thr					
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<210> 25

<211> 1461

<212> DNA

<213> Saccharopolyspora spinosa

<220>

<221> CDS

<222> (1) .. (1458)

<223> ORF10; 2,3-Dehydratase

<400> 25

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agc aac aac acg cgg cgg ttc gtc gac tct gcg ctg agc gct tgc aat	96
Ser Asn Asn Thr Arg Arg Phe Val Asp Ser Ala Leu Ser Ala Cys Asn	
20 25 30	
ggc atg att ccg acc acg gag ttc cac tgc tgg ctc gcc gat cgg ctg	144
Gly Met Ile Pro Thr Thr Glu Phe His Cys Trp Leu Ala Asp Arg Leu	
35 40 45	
ggc gag aac agc ttc gag acc aat cgc atc ccg ttc gac cgc ctg tcg	192
Gly Glu Asn Ser Phe Glu Thr Asn Arg Ile Pro Phe Asp Arg Leu Ser	
50 55 60	
aaa tgg aaa ttc gat gcc agc acg gag aac ctg gtt cat gcc gac ggt	240
Lys Trp Lys Phe Asp Ala Ser Thr Glu Asn Leu Val His Ala Asp Gly	
65 70 75 80	
agg ttc ttc acg gta gaa ggc ctg cag gtc gag acc aac tat ggc gcg	288
Arg Phe Phe Thr Val Glu Gly Leu Gln Val Glu Thr Asn Tyr Gly Ala	
85 90 95	
gca ccc agc tgg cac cag ccg atc atc aac cag gct gaa gta ggt atc	336
Ala Pro Ser Trp His Gln Pro Ile Ile Asn Gln Ala Glu Val Gly Ile	
100 105 110	
ctc ggc att ctc gtc aag gag atc gac ggc gtg ctg cac tgc ctc atg	384
Leu Gly Ile Leu Val Lys Glu Ile Asp Gly Val Leu His Cys Leu Met	
115 120 125	
tca gca aag atg gaa ccg ggc aac gtc aac gtc ctg cag ctc tcg ccg	432
Ser Ala Lys Met Glu Pro Gly Asn Val Asn Val Leu Gln Leu Ser Pro	
130 135 140	
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Thr Val Gln Ala Thr Arg Ser Asn Tyr Thr Gln Ala His Arg Gly Ser	
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Val Pro Pro Tyr Val Asp Tyr Phe Leu Gly Arg Gly Arg Gly Arg Val	
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ctg gta gac gtg ctc cag tct gaa cag ggg tcc tgg ttc tac cgg aag	576
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180 185 190	
cgc aac cgg aac atg gtg gtg gaa gtc cag gag gaa gtg cca gtc ctg	624
Arg Asn Arg Asn Met Val Val Glu Val Gln Glu Glu Val Pro Val Leu	
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Gln Asp Asn Ile Val Asn Met Asp Thr Arg Thr Val Leu Ser Cys Ile	
225 230 235 240	
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Pro Phe His Asp Ser Ala Thr Gly Pro Glu Leu Ala Ala Ser Glu Glu	
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Pro Phe Arg Gln Ala Val Ala Arg Ser Leu Ser His Gly Ile Asp Ser	
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Ser Ser Ile Ser Glu Ala Val Gly Trp Phe Glu Glu Ala Lys Ala Arg	
275 280 285	
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Tyr Arg Leu Arg Ala Thr Arg Val Pro Leu Ser Arg Val Asp Lys Trp	
290 295 300	
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Tyr Arg Thr Asp Thr Glu Ile Ala His Gln Asp Gly Lys Tyr Phe Ala	
305 310 315 320	
gtg atc gcg gtg tcg gtg tcc gcg acc aat cgt gag gtc gcc agc tgg	1008
Val Ile Ala Val Ser Val Ser Ala Thr Asn Arg Glu Val Ala Ser Trp	
325 330 335	
acg cag ccg atg atc gaa ccg cga gaa caa ggt gag atc gca ctg ttg	1056
Thr Gln Pro Met Ile Glu Pro Arg Glu Gln Gly Glu Ile Ala Leu Leu	
340 345 350	
gtc aag cgg atc ggc gga gtg ctg cac ggt ttg gtc cac gct cgg gtg	1104
Val Lys Arg Ile Gly Gly Val Leu His Gly Leu Val His Ala Arg Val	
355 360 365	
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Glu Ala Gly Tyr Lys Trp Thr Ala Glu Ile Ala Pro Thr Val Gln Cys	
370 375 380	
agt gtg gcc aac tac caa agc acc ccg tcg aac gac tgg ccg ccg ttc	1200
Ser Val Ala Asn Tyr Gln Ser Thr Pro Ser Asn Asp Trp Pro Pro Phe	
385 390 395 400	

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 Leu Asp Asp Val Leu Thr Ala Asp Pro Glu Thr Val Arg Tyr Glu Ser
 405 410 415

atc ctg tcc gaa gaa ggc ggt cgg ttc tac cag gcg cag aac agg tac 1296
 Ile Leu Ser Glu Glu Gly Gly Arg Phe Tyr Gln Ala Gln Asn Arg Tyr
 420 425 430

cgg atc atc gag gtg cat gag gac ttc gcg gca cga cct ccc agc gac 1344
 Arg Ile Ile Glu Val His Glu Asp Phe Ala Ala Arg Pro Pro Ser Asp
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 Phe Arg Trp Met Thr Leu Gly Gln Leu Gly Glu Leu Leu Arg Ser Thr
 450 455 460

cac ttc ttg aac atc cag gcg cgc agc ttg gtc gcc tcc ctg cat agc 1440
 His Phe Leu Asn Ile Gln Ala Arg Ser Leu Val Ala Ser Leu His Ser
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 Leu Trp Ala Leu Gly Arg
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<211> 486

<212> PRT

<213> Saccharopolyspora spinosa

<400> 26

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Gly Met Ile Pro Thr Thr Glu Phe His Cys Trp Leu Ala Asp Arg Leu
 35 40 45

Gly Glu Asn Ser Phe Glu Thr Asn Arg Ile Pro Phe Asp Arg Leu Ser
 50 55 60

Lys Trp Lys Phe Asp Ala Ser Thr Glu Asn Leu Val His Ala Asp Gly
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1				5					10					15		

tca	tcg	ctg	ttg	cgt	cga	ctc	gga	ttc	cgc	cgt	gac	cgg	gac	gat	gcc	96
Ser	Ser	Leu	Leu	Arg	Arg	Leu	Gly	Phe	Arg	Arg	Asp	Arg	Asp	Asp	Ala	

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Leu Ile Ser Pro Glu Val Cys Ala Pro Thr Asp Phe Arg Arg Gly Ser				
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tgg cgc ccg ctg agc aac gac tac cgt gcg gtc gag aca tac cgc tgt				240
Trp Arg Pro Leu Ser Asn Asp Tyr Arg Ala Val Glu Thr Tyr Arg Cys				
	65	70	75	80
gcg cca gga gcg aag gtg ggt tgc ccg atc acc gtg ctg gtg gta gat				288
Ala Pro Gly Ala Lys Val Gly Cys Pro Ile Thr Val Leu Val Val Asp				
	85	90	95	
gcc gag ccg aag gtc acc ttg gat gag gcg gaa gcc tgg cga gag cac				336
Ala Glu Pro Lys Val Thr Leu Asp Glu Ala Glu Ala Trp Arg Glu His				
	100	105	110	
acc gag gcc gtg gcc gac gtc cgt gtc ttc tcc ggc ggg cat ttc ttc				384
Thr Glu Ala Val Ala Asp Val Arg Val Phe Ser Gly Gly His Phe Phe				
	115	120	125	
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<211> 146

<212> PRT

<213> Saccharopolyspora spinosa

<400> 28

Val Ser Asn Val Trp Pro Glu Thr Trp Thr Pro Gly Phe Gly Arg Cys

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5

10

15

Ser Ser Leu Leu Arg Arg Leu Gly Phe Arg Arg Asp Arg Asp Ala

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25

30

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Arg Arg Val Pro Lys Ser Asp Ser Cys Pro Glu Ser Ser Asn Gly Val
 35 40 45

Leu Ile Ser Pro Glu Val Cys Ala Pro Thr Asp Phe Arg Arg Gly Ser
 50 55 60

Trp Arg Pro Leu Ser Asn Asp Tyr Arg Ala Val Glu Thr Tyr Arg Cys
 65 70 75 80

Ala Pro Gly Ala Lys Val Gly Cys Pro Ile Thr Val Leu Val Val Asp
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Ala Glu Pro Lys Val Thr Leu Asp Glu Ala Glu Ala Trp Arg Glu His
 100 105 110

Thr Glu Ala Val Ala Asp Val Arg Val Phe Ser Gly Gly His Phe Phe
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Met Thr Glu Arg Gln Asp Glu Val Leu Ala Val Leu Thr Gly Gly Ser
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Leu Arg
 145

<210> 29

<211> 1320

<212> DNA

<213> Saccharopolyspora spinosa

<220>

<221> CDS

<222> (1)..(1317)

<223> ORF12; Glycosyltransferase

<400> 29

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ctg gtg ccg ttg gcg tgg gcg ttg cgt gcc gcg ggg cac gag gtc cgt 96
 Leu Val Pro Leu Ala Trp Ala Leu Arg Ala Ala Gly His Glu Val Arg
 20 25 30

gtc gcc atc tgc ccg aat atg gtg tcg atg gtc acc gga gca gga ctc 144
 Val Ala Ile Cys Pro Asn Met Val Ser Met Val Thr Gly Ala Gly Leu

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aag aac gaa ctc gtt ctc ggc agc ggg gtc tcg ttc gac gag aag ggg			240
Lys Asn Glu Leu Val Leu Gly Ser Gly Val Ser Phe Asp Glu Lys Gly			
65	70	75	80
cgg cat ccg gaa ctc ttc gac gag ctg ctg tca atc aac tcc ggc aga			288
Arg His Pro Glu Leu Phe Asp Glu Leu Leu Ser Ile Asn Ser Gly Arg			
85	90	95	
gac acg gac gcc gtg gag caa ctc cac ctt gtg gat gac cga tcg ctg			336
Asp Thr Asp Ala Val Glu Gln Leu His Leu Val Asp Asp Arg Ser Leu			
100	105	110	
gac gat ctc atg ggg ttc gcc gag aaa tgg cag cct gat ctc gtt gtg			384
Asp Asp Leu Met Gly Phe Ala Glu Lys Trp Gln Pro Asp Leu Val Val			
115	120	125	
tgg gac gct atg gtg tgt tcg ggg cca gtt gtg gcg cga gcg ctc ggc			432
Trp Asp Ala Met Val Cys Ser Gly Pro Val Val Ala Arg Ala Leu Gly			
130	135	140	
gca cga cac gtg cgg atg ctc gtc gcc ctc gat gtg tcg ggg tgg ctg			480
Ala Arg His Val Arg Met Leu Val Ala Leu Asp Val Ser Gly Trp Leu			
145	150	155	160
cgg tcc ggt ttc ctc gaa tac cag gaa tcg aag ccg cct gag cag cgc			528
Arg Ser Gly Phe Leu Glu Tyr Gln Glu Ser Lys Pro Pro Glu Gln Arg			
165	170	175	
gtc gac ccg ctc ggg acg tgg ctg gga gcg aag ctc gcc aag ttc gga			576
Val Asp Pro Leu Gly Thr Trp Leu Gly Ala Lys Leu Ala Lys Phe Gly			
180	185	190	
gcc acg ttc gat gaa gag atc gtg acg ggc caa gcg acc ata gat ccg			624
Ala Thr Phe Asp Glu Glu Ile Val Thr Gly Gln Ala Thr Ile Asp Pro			
195	200	205	
att cca tcc tgg atg cgc ctg cct gtg gac ttg gac tac atc tcg atg			672
Ile Pro Ser Trp Met Arg Leu Pro Val Asp Leu Asp Tyr Ile Ser Met			
210	215	220	
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Arg Phe Val Pro Tyr Asn Gly Pro Ala Val Leu Pro Glu Trp Leu Arg			

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cgg cgg ctg agc agg gtg acc gaa cag tac ggg gag caa agt gac cag				816
Arg Arg Leu Ser Arg Val Thr Glu Gln Tyr Gly Glu Gln Ser Asp Gln				
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Glu Gln Ala Met Val Glu Arg Leu Leu Arg Gly Ala Ala Arg Leu Asp				
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Leu Leu Glu Ser Cys Ser Val Ile Ile His His Gly Ser Thr Thr Thr				
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Ala Leu Ile Arg Arg Glu Ile Glu Glu Ser Pro Ser Pro His Asp Ile				
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 <213> *Saccharopolyspora spinosa*

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 Lys Asn Glu Leu Val Leu Gly Ser Gly Val Ser Phe Asp Glu Lys Gly
 65 70 75 80
 Arg His Pro Glu Leu Phe Asp Glu Leu Leu Ser Ile Asn Ser Gly Arg
 85 90 95
 Asp Thr Asp Ala Val Glu Gln Leu His Leu Val Asp Asp Arg Ser Leu
 100 105 110
 Asp Asp Leu Met Gly Phe Ala Glu Lys Trp Gln Pro Asp Leu Val Val
 115 120 125
 Trp Asp Ala Met Val Cys Ser Gly Pro Val Val Ala Arg Ala Leu Gly
 130 135 140
 Ala Arg His Val Arg Met Leu Val Ala Leu Asp Val Ser Gly Trp Leu
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 Arg Ser Gly Phe Leu Glu Tyr Gln Glu Ser Lys Pro Pro Glu Gln Arg
 165 170 175
 Val Asp Pro Leu Gly Thr Trp Leu Gly Ala Lys Leu Ala Lys Phe Gly
 180 185 190

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 Ile Pro Ser Trp Met Arg Leu Pro Val Asp Leu Asp Tyr Ile Ser Met
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 245 250 255
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 260 265 270
 Glu Gln Ala Met Val Glu Arg Leu Leu Arg Gly Ala Ala Arg Leu Asp
 275 280 285
 Val Glu Val Ile Ala Thr Leu Ser Asp Asp Glu Val Arg Glu Met Gly
 290 295 300
 Glu Leu Pro Ser Asn Val Arg Val His Glu Tyr Val Pro Leu Asn Glu
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 Leu Leu Glu Ser Cys Ser Val Ile Ile His His Gly Ser Thr Thr Thr
 325 330 335
 Gln Glu Thr Ala Thr Val Asn Gly Val Pro Gln Leu Ile Leu Pro Gly
 340 345 350
 Thr Phe Trp Asp Glu Ser Arg Arg Ala Glu Leu Leu Ala Asp Arg Gly
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 Ala Gly Leu Val Leu Asp Pro Ala Thr Phe Thr Glu Asp Asp Val Arg
 370 375 380
 Gly Gln Leu Ala Arg Leu Leu Asp Glu Pro Ser Phe Ala Ala Asn Ala
 385 390 395 400
 Ala Leu Ile Arg Arg Glu Ile Glu Glu Ser Pro Ser Pro His Asp Ile
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<212> DNA

<213> Saccharopolyspora spinosa

<220>

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<223> ORF13; 3,4-Dehydratase

<400> 31

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Thr Ser Cys Asp Asp Thr Cys Ala Thr Ala Thr Glu Met Val Pro Asp
             20             25             30

gcc aag gac cgg ata ttg gca tcc gta cgc gat tac cac cgc gaa cag   144
Ala Lys Asp Arg Ile Leu Ala Ser Val Arg Asp Tyr His Arg Glu Gln
             35             40             45

gaa tcc ccg acc ttc gtg gct gga tcg acg ccg atc cgg cca tcg ggc   192
Glu Ser Pro Thr Phe Val Ala Gly Ser Thr Pro Ile Arg Pro Ser Gly
             50             55             60

gcc gtg ctc gac gag gac gac cgg gtg gca ctg gtg gaa gcc gcg ctg   240
Ala Val Leu Asp Glu Asp Arg Val Ala Leu Val Glu Ala Ala Leu
             65             70             75             80

gag ctc cgg atc gcc gcg ggc ggg aat gca cgg cga ttc gag agc gag   288
Glu Leu Arg Ile Ala Ala Gly Gly Asn Ala Arg Arg Phe Glu Ser Glu
             85             90             95

ttc gcc cgc ttc ttc ggc ctc cgc aag gct cat ctc gtc aac tcc ggt   336
Phe Ala Arg Phe Phe Gly Leu Arg Lys Ala His Leu Val Asn Ser Gly
             100            105            110

tcg tcg gcc aat ctc ctg gca ctg agt tcg ctt acc tcc ccc aaa ctc   384
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Val Phe Val Asp Val Glu Leu Gly Thr Tyr Asn Ala Thr Pro Asp Arg			
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Ile Lys Ala Ala Val Thr Glu Arg Thr Arg Ala Ile Met Leu Ala His			
	180	185	190
acc ctg ggc aac ccc ttc gcc gct gac gaa atc gcg gag atc gca aaa			624
Thr Leu Gly Asn Pro Phe Ala Ala Asp Glu Ile Ala Glu Ile Ala Lys			
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gaa cac gag ctg ttc ctc gtc gaa gac aac tgt gat gcg gtg gga tcc			672
Glu His Glu Leu Phe Leu Val Glu Asp Asn Cys Asp Ala Val Gly Ser			
	210	215	220
acc tac cgg gga cgg ctg acc gga acc ttc ggc gac ctg aca acg gtc			720
Thr Tyr Arg Gly Arg Leu Thr Gly Thr Phe Gly Asp Leu Thr Thr Val			
	225	230	235
agc ttc tat cct gcc cat cac atc acc agc ggc gag ggt ggc tgc gtg			768
Ser Phe Tyr Pro Ala His His Ile Thr Ser Gly Glu Gly Gly Cys Val			
	245	250	255
ttg acc ggc agc ctg gaa ttg gct cgc atc atc gag tcg ctg cgt gac			816
Leu Thr Gly Ser Leu Glu Leu Ala Arg Ile Ile Glu Ser Leu Arg Asp			
	260	265	270
tgg gga cgg gat tgc tgg tgc gag ccc ggc gtg gac aac acc tgc cgc			864
Trp Gly Arg Asp Cys Trp Cys Glu Pro Gly Val Asp Asn Thr Cys Arg			
	275	280	285
aag agg ttc gac tac cac ctc ggt acc ctt cca ccg ggc tac gac cac			912
Lys Arg Phe Asp Tyr His Leu Gly Thr Leu Pro Pro Gly Tyr Asp His			
	290	295	300
aag tac acg ttc tcc cac gtc ggt tac aac ctc aag acc acc gac ctg			960
Lys Tyr Thr Phe Ser His Val Gly Tyr Asn Leu Lys Thr Thr Asp Leu			
	305	310	315
cag gcc gca ctt gcg ctg agc cag ttg agc aag att tcc gca ttc ggg			1008
Gln Ala Ala Leu Ala Leu Ser Gln Leu Ser Lys Ile Ser Ala Phe Gly			

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Leu Pro Gly Leu Leu Leu Pro Val Ala Thr Pro His Ser Asp Pro Ser			
355	360	365	
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Trp Phe Gly Phe Ala Ile Thr Ile Ser Ala Asp Ala Gly Phe Thr Arg			
370	375	380	
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Ala Ala Leu Val Asn Phe Leu Glu Ser Arg Asn Ile Gly Thr Arg Leu			
385	390	395	400
ctg ttc ggc ggt aac atc acc cgg cac ccg gcc ttc gag cag gtg cgg			1248
Leu Phe Gly Gly Asn Ile Thr Arg His Pro Ala Phe Glu Gln Val Arg			
405	410	415	
tac cgg atc gcc gac gcg ctc acc aac agc gac atc gtc acc gac cga			1296
Tyr Arg Ile Ala Asp Ala Leu Thr Asn Ser Asp Ile Val Thr Asp Arg			
420	425	430	
acc ttc tgg gtc ggc gtc tac cca ggc ata acg gac caa atg atc gac			1344
Thr Phe Trp Val Gly Val Tyr Pro Gly Ile Thr Asp Gln Met Ile Asp			
435	440	445	
tac gtc gtc gaa tca atc gct gaa ttc gtg gcc aag agt tcc tag			1389
Tyr Val Val Glu Ser Ile Ala Glu Phe Val Ala Lys Ser Ser			
450	455	460	

<210> 32

<211> 462

<212> PRT

<213> Saccharopolyspora spinosa

<400> 32

Met	Gln	Ser	Arg	Lys	Thr	Arg	Ala	Leu	Gly	Lys	Gly	Arg	Ala	Arg	Val
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Thr	Ser	Cys	Asp	Asp	Thr	Cys	Ala	Thr	Ala	Thr	Glu	Met	Val	Pro	Asp
			20					25					30		

Ala Lys Asp Arg Ile Leu Ala Ser Val Arg Asp Tyr His Arg Glu Gln

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Glu Ser Pro Thr Phe Val Ala Gly Ser Thr Pro Ile Arg Pro Ser Gly		
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Ala Val Leu Asp Glu Asp Asp Arg Val Ala Leu Val Glu Ala Ala Leu		
65	70	75
80		
Glu Leu Arg Ile Ala Ala Gly Gly Asn Ala Arg Arg Phe Glu Ser Glu		
85	90	95
Phe Ala Arg Phe Phe Gly Leu Arg Lys Ala His Leu Val Asn Ser Gly		
100	105	110
Ser Ser Ala Asn Leu Leu Ala Leu Ser Ser Leu Thr Ser Pro Lys Leu		
115	120	125
Gly Glu Ala Arg Leu Arg Pro Gly Asp Glu Val Ile Thr Ala Ala Val		
130	135	140
Gly Phe Pro Thr Thr Ile Asn Pro Ala Val Gln Asn Gly Leu Val Pro		
145	150	155
160		
Val Phe Val Asp Val Glu Leu Gly Thr Tyr Asn Ala Thr Pro Asp Arg		
165	170	175
Ile Lys Ala Ala Val Thr Glu Arg Thr Arg Ala Ile Met Leu Ala His		
180	185	190
Thr Leu Gly Asn Pro Phe Ala Ala Asp Glu Ile Ala Glu Ile Ala Lys		
195	200	205
Glu His Glu Leu Phe Leu Val Glu Asp Asn Cys Asp Ala Val Gly Ser		
210	215	220
Thr Tyr Arg Gly Arg Leu Thr Gly Thr Phe Gly Asp Leu Thr Thr Val		
225	230	235
240		
Ser Phe Tyr Pro Ala His His Ile Thr Ser Gly Glu Gly Gly Cys Val		
245	250	255
Leu Thr Gly Ser Leu Glu Leu Ala Arg Ile Ile Glu Ser Leu Arg Asp		
260	265	270
Trp Gly Arg Asp Cys Trp Cys Glu Pro Gly Val Asp Asn Thr Cys Arg		
275	280	285
Lys Arg Phe Asp Tyr His Leu Gly Thr Leu Pro Pro Gly Tyr Asp His		

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290	295	300
Lys Tyr Thr Phe Ser His Val Gly Tyr Asn Leu Lys Thr Thr Asp Leu		
305	310	315 320
Gln Ala Ala Leu Ala Leu Ser Gln Leu Ser Lys Ile Ser Ala Phe Gly		
325	330	335
Ser Ala Arg Arg Arg Asn Trp Arg Arg Leu Arg Glu Gly Leu Ser Gly		
340	345	350
Leu Pro Gly Leu Leu Leu Pro Val Ala Thr Pro His Ser Asp Pro Ser		
355	360	365
Trp Phe Gly Phe Ala Ile Thr Ile Ser Ala Asp Ala Gly Phe Thr Arg		
370	375	380
Ala Ala Leu Val Asn Phe Leu Glu Ser Arg Asn Ile Gly Thr Arg Leu		
385	390	395 400
Leu Phe Gly Gly Asn Ile Thr Arg His Pro Ala Phe Glu Gln Val Arg		
405	410	415
Tyr Arg Ile Ala Asp Ala Leu Thr Asn Ser Asp Ile Val Thr Asp Arg		
420	425	430
Thr Phe Trp Val Gly Val Tyr Pro Gly Ile Thr Asp Gln Met Ile Asp		
435	440	445
Tyr Val Val Glu Ser Ile Ala Glu Phe Val Ala Lys Ser Ser		
450	455	460

<210> 33
 <211> 1158
 <212> DNA
 <213> Saccharopolyspora spinosa

<220>
 <221> CDS
 <222> (1) .. (1155)
 <223> ORF14; 4-Aminotransferase

<400> 33
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 1 5 10 15

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atc gcg gag gtg ttc gcc tcc aac tgg atc ggg ctc ggg ccg cgc acc	96
Ile Ala Glu Val Phe Ala Ser Asn Trp Ile Gly Leu Gly Pro Arg Thr	
20 25 30	
cgg acg ttc gag gcc gaa ttc gcc cac cac ctg gga gtg gat ccc gaa	144
Arg Thr Phe Glu Ala Glu Phe Ala His His Leu Gly Val Asp Pro Glu	
35 40 45	
cag gtc gtg ttc ctc aac tcg ggg act gcc gcg ctg ttc ctt acc gtg	192
Gln Val Val Phe Leu Asn Ser Gly Thr Ala Ala Leu Phe Leu Thr Val	
50 55 60	
cag gtg ctc gac ctc ggc cca ggc gac gac gtg gta ctt cct tcg ata	240
Gln Val Leu Asp Leu Gly Pro Gly Asp Asp Val Val Leu Pro Ser Ile	
65 70 75 80	
agc ttc gtg gcg gcg gcc aac gcc atc gca tcc tcc ggt gcc cgc ccg	288
Ser Phe Val Ala Ala Ala Asn Ala Ile Ala Ser Ser Gly Ala Arg Pro	
85 90 95	
gtg ttc tgc gac gtc gac ccc cgg acg ttg aac ccc acg ctg gat gat	336
Val Phe Cys Asp Val Asp Pro Arg Thr Leu Asn Pro Thr Leu Asp Asp	
100 105 110	
gtg gcg agg gcc atc acg ccg gcg acc aag gcc gta ttg ctg ctc cac	384
Val Ala Arg Ala Ile Thr Pro Ala Thr Lys Ala Val Leu Leu Leu His	
115 120 125	
tat gga gga tcg ccg gga gaa gtc acc gcg atc gcc gat ttc tgc cgt	432
Tyr Gly Gly Ser Pro Gly Glu Val Thr Ala Ile Ala Asp Phe Cys Arg	
130 135 140	
gaa aag ggc ctc atg ctc atc gag gac tcc gcc tgc gcg gtg gca tcg	480
Glu Lys Gly Leu Met Leu Ile Glu Asp Ser Ala Cys Ala Val Ala Ser	
145 150 155 160	
tcc gtg cac ggc acc gct tgc gga acc ttt ggt gac ctg gcc acg tgg	528
Ser Val His Gly Thr Ala Cys Gly Thr Phe Gly Asp Leu Ala Thr Trp	
165 170 175	
agt ttc gat gcg atg aag atc ctg gtc acc ggg gat ggg ggc atg ttc	576
Ser Phe Asp Ala Met Lys Ile Leu Val Thr Gly Asp Gly Gly Met Phe	
180 185 190	
tac gcg gcg gat ccg gag ctg gcg cac cgc gca aga cga ctc gcc tac	624
Tyr Ala Ala Asp Pro Glu Leu Ala His Arg Ala Arg Leu Ala Tyr	
195 200 205	

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cac ggt ctt gag cag atg agc gga ttc gat tcg gcc aag tct tcc aac	672
His Gly Leu Glu Gln Met Ser Gly Phe Asp Ser Ala Lys Ser Ser Asn	
210 215 220	
cgc tgg tgg gat att cgc gtc gaa gac atc ggc cag cgg ctg atc ggg	720
Arg Trp Trp Asp Ile Arg Val Glu Asp Ile Gly Gln Arg Leu Ile Gly	
225 230 235 240	
aac gac atg acg gca gcg ctt ggc agc gtg cag ctg cgc aaa ctg cca	768
Asn Asp Met Thr Ala Ala Leu Gly Ser Val Gln Leu Arg Lys Leu Pro	
245 250 255	
gaa ttc atc aac agg cgt aga gaa atc gct acg cag tac gac cgg ttg	816
Glu Phe Ile Asn Arg Arg Arg Glu Ile Ala Thr Gln Tyr Asp Arg Leu	
260 265 270	
ctt tcc gat gtg ccg ggt gtc ctc cta ccg ccg acg cta ccg gat ggg	864
Leu Ser Asp Val Pro Gly Val Leu Leu Pro Pro Thr Leu Pro Asp Gly	
275 280 285	
cac gtc tcg tca cac tac ttc tac tgg gtc cag ctg gct ccg gag atc	912
His Val Ser Ser His Tyr Phe Tyr Trp Val Gln Leu Ala Pro Glu Ile	
290 295 300	
cgc gac cag gtg gcg cag caa atg ctg gaa cgc ggc atc tac acg agc	960
Arg Asp Gln Val Ala Gln Gln Met Leu Glu Arg Gly Ile Tyr Thr Ser	
305 310 315 320	
tac cgc tac ccg ccc ctg cac aag gtc ccc atc tac cgc gcg gac tgc	1008
Tyr Arg Tyr Pro Pro Leu His Lys Val Pro Ile Tyr Arg Ala Asp Cys	
325 330 335	
aag ctg cct tct gcg gag cac gcc tgc cgc aga aca ctc ctg cta cca	1056
Lys Leu Pro Ser Ala Glu His Ala Cys Arg Arg Thr Leu Leu Leu Pro	
340 345 350	
ctg cac cca agc ctt gac gac gcc gag gtg cgc acg gtg gct gac gag	1104
Leu His Pro Ser Leu Asp Asp Ala Glu Val Arg Thr Val Ala Asp Glu	
355 360 365	
ttc cag aag gcc gtc gaa cac cac atc agc caa aga tca cca ctc cga	1152
Phe Gln Lys Ala Val Glu His His Ile Ser Gln Arg Ser Pro Leu Arg	
370 375 380	
aag tga	1158
Lys	
385	

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<210> 34

<211> 385

<212> PRT

<213> Saccharopolyspora spinosa

<400> 34

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Ile Ala Glu Val Phe Ala Ser Asn Trp Ile Gly Leu Gly Pro Arg Thr
 20 25 30

Arg Thr Phe Glu Ala Glu Phe Ala His His Leu Gly Val Asp Pro Glu
 35 40 45

Gln Val Val Phe Leu Asn Ser Gly Thr Ala Ala Leu Phe Leu Thr Val
 50 55 60

Gln Val Leu Asp Leu Gly Pro Gly Asp Asp Val Val Leu Pro Ser Ile
 65 70 75 80

Ser Phe Val Ala Ala Ala Asn Ala Ile Ala Ser Ser Gly Ala Arg Pro
 85 90 95

Val Phe Cys Asp Val Asp Pro Arg Thr Leu Asn Pro Thr Leu Asp Asp
 100 105 110

Val Ala Arg Ala Ile Thr Pro Ala Thr Lys Ala Val Leu Leu Leu His
 115 120 125

Tyr Gly Gly Ser Pro Gly Glu Val Thr Ala Ile Ala Asp Phe Cys Arg
 130 135 140

Glu Lys Gly Leu Met Leu Ile Glu Asp Ser Ala Cys Ala Val Ala Ser
 145 150 155 160

Ser Val His Gly Thr Ala Cys Gly Thr Phe Gly Asp Leu Ala Thr Trp
 165 170 175

Ser Phe Asp Ala Met Lys Ile Leu Val Thr Gly Asp Gly Gly Met Phe
 180 185 190

Tyr Ala Ala Asp Pro Glu Leu Ala His Arg Ala Arg Arg Leu Ala Tyr
 195 200 205

His Gly Leu Glu Gln Met Ser Gly Phe Asp Ser Ala Lys Ser Ser Asn

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210	215	220
Arg Trp Trp Asp Ile Arg Val Glu Asp Ile Gly Gln Arg Leu Ile Gly		
225	230	235 240
Asn Asp Met Thr Ala Ala Leu Gly Ser Val Gln Leu Arg Lys Leu Pro		
245	250	255
Glu Phe Ile Asn Arg Arg Arg Glu Ile Ala Thr Gln Tyr Asp Arg Leu		
260	265	270
Leu Ser Asp Val Pro Gly Val Leu Leu Pro Pro Thr Leu Pro Asp Gly		
275	280	285
His Val Ser Ser His Tyr Phe Tyr Trp Val Gln Leu Ala Pro Glu Ile		
290	295	300
Arg Asp Gln Val Ala Gln Gln Met Leu Glu Arg Gly Ile Tyr Thr Ser		
305	310	315 320
Tyr Arg Tyr Pro Pro Leu His Lys Val Pro Ile Tyr Arg Ala Asp Cys		
325	330	335
Lys Leu Pro Ser Ala Glu His Ala Cys Arg Arg Thr Leu Leu Leu Pro		
340	345	350
Leu His Pro Ser Leu Asp Asp Ala Glu Val Arg Thr Val Ala Asp Glu		
355	360	365
Phe Gln Lys Ala Val Glu His His Ile Ser Gln Arg Ser Pro Leu Arg		
370	375	380
Lys		
385		

<210> 35

<211> 750

<212> DNA

<213> Saccharopolyspora spinosa

<220>

<221> CDS

<222> (1) .. (747)

<223> ORF15; N-Dimethyltransferase

<400> 35

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1 5 10 15	
cca gat cat gcc gac atc tac gac gcg atc cac tcc gcg cgt ggc cgg	96
Pro Asp His Ala Asp Ile Tyr Asp Ala Ile His Ser Ala Arg Gly Arg	
20 25 30	
gac tgg gca gcc gag gcc ggg gaa gta gtc cag ctc gta cgc acc agg	144
Asp Trp Ala Ala Glu Ala Gly Glu Val Val Gln Leu Val Arg Thr Arg	
35 40 45	
ctg ccc gaa gca cag tcc cta ctc gac gtc gcc tgt ggg acc ggg gcg	192
Leu Pro Glu Ala Gln Ser Leu Leu Asp Val Ala Cys Gly Thr Gly Ala	
50 55 60	
cac cta gag cga ttc cgt gcc gaa tac gcg aag gtc gcg ggg ctt gaa	240
His Leu Glu Arg Phe Arg Ala Glu Tyr Ala Lys Val Ala Gly Leu Glu	
65 70 75 80	
ctg tcc gat gcg atg cgg gag atc gcg atc aga cga gtc cct gag gta	288
Leu Ser Asp Ala Met Arg Glu Ile Ala Ile Arg Arg Val Pro Glu Val	
85 90 95	
ccg att cac atc ggt gac atc cgc gat ttc gac ctc ggc gag cca ttc	336
Pro Ile His Ile Gly Asp Ile Arg Asp Phe Asp Leu Gly Glu Pro Phe	
100 105 110	
gac gtc atc acc tgc ctg tgc ttt acc gcg gct tac atg cgg acc gtt	384
Asp Val Ile Thr Cys Leu Cys Phe Thr Ala Ala Tyr Met Arg Thr Val	
115 120 125	
gac gac ctg cga cgc gtg acg cgg aac atg gcc cgg cac ctg gcc cct	432
Asp Asp Leu Arg Arg Val Thr Arg Asn Met Ala Arg His Leu Ala Pro	
130 135 140	
ggg gga gtc gcg gtc atc gaa ccc tgg tgg ttt ccc gac aag ttc atc	480
Gly Gly Val Ala Val Ile Glu Pro Trp Trp Phe Pro Asp Lys Phe Ile	
145 150 155 160	
gac ggg ttc gtc acc gga gcc gtc gcg cac cac ggc gag cgg gtg atc	528
Asp Gly Phe Val Thr Gly Ala Val Ala His His Gly Glu Arg Val Ile	
165 170 175	
agc cgg cta tcg cac tcg gtc ctg gag ggc cgt acg agc cgg atg acc	576
Ser Arg Leu Ser His Ser Val Leu Glu Gly Arg Thr Ser Arg Met Thr	
180 185 190	

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gtc cgc tac aca gtc gcc gaa ccc acc ggg atc cgg gac ttc aca gag 624
 Val Arg Tyr Thr Val Ala Glu Pro Thr Gly Ile Arg Asp Phe Thr Glu
 195 200 205

ttc gaa atc ctc tcg ctg ttc act gag gac gag tac acc gcc gcg ctc 672
 Phe Glu Ile Leu Ser Leu Phe Thr Glu Asp Glu Tyr Thr Ala Ala Leu
 210 215 220

gaa gac gca ggg atc cgc gcg gaa tac ctt cct gga gca ccg aac ggc 720
 Glu Asp Ala Gly Ile Arg Ala Glu Tyr Leu Pro Gly Ala Pro Asn Gly
 225 230 235 240

cga ggc ctg ttc gtc gga atc cgc aac tga 750
 Arg Gly Leu Phe Val Gly Ile Arg Asn
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<210> 36

<211> 249

<212> PRT

<213> Saccharopolyspora spinosa

<400> 36

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Pro Asp His Ala Asp Ile Tyr Asp Ala Ile His Ser Ala Arg Gly Arg
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Asp Trp Ala Ala Glu Ala Gly Glu Val Val Gln Leu Val Arg Thr Arg
 35 40 45

Leu Pro Glu Ala Gln Ser Leu Leu Asp Val Ala Cys Gly Thr Gly Ala
 50 55 60

His Leu Glu Arg Phe Arg Ala Glu Tyr Ala Lys Val Ala Gly Leu Glu
 65 70 75 80

Leu Ser Asp Ala Met Arg Glu Ile Ala Ile Arg Arg Val Pro Glu Val
 85 90 95

Pro Ile His Ile Gly Asp Ile Arg Asp Phe Asp Leu Gly Glu Pro Phe
 100 105 110

Asp Val Ile Thr Cys Leu Cys Phe Thr Ala Ala Tyr Met Arg Thr Val
 115 120 125

Asp Asp Leu Arg Arg Val Thr Arg Asn Met Ala Arg His Leu Ala Pro

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130	135	140
Gly Gly Val Ala Val Ile Glu Pro Trp Trp Phe Pro Asp Lys Phe Ile		
145	150	155 160
Asp Gly Phe Val Thr Gly Ala Val Ala His His Gly Glu Arg Val Ile		
165	170	175
Ser Arg Leu Ser His Ser Val Leu Glu Gly Arg Thr Ser Arg Met Thr		
180	185	190
Val Arg Tyr Thr Val Ala Glu Pro Thr Gly Ile Arg Asp Phe Thr Glu		
195	200	205
Phe Glu Ile Leu Ser Leu Phe Thr Glu Asp Glu Tyr Thr Ala Ala Leu		
210	215	220
Glu Asp Ala Gly Ile Arg Ala Glu Tyr Leu Pro Gly Ala Pro Asn Gly		
225	230	235 240
Arg Gly Leu Phe Val Gly Ile Arg Asn		
245		

<210> 37
 <211> 726
 <212> DNA
 <213> Saccharopolyspora spinosa

<220>
 <221> CDS
 <222> (1)..(723)
 <223> ORF16; 3,4-Reduktase

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1 5 10 15	
gga tac gag atc gcg gcc ggg ctc ggc gcg ctg ggg tgg agc gtc gga	96
Gly Tyr Glu Ile Ala Ala Gly Leu Gly Ala Leu Gly Trp Ser Val Gly	
20 25 30	
atc ggg gca cgg gac cac cag cgc ggg gag gat gcc gtg gcg aaa ttg	144
Ile Gly Ala Arg Asp His Gln Arg Gly Glu Asp Ala Val Ala Lys Leu	
35 40 45	

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cgt gcg gac ggc gtc gat gcg ttc gcg gta tcc ctg gac gtg aca gac	192
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50 55 60	
gac gcg agc gtc gcg gct gct gcg gct ctg ctc gag gag cgc gcc ggc	240
Asp Ala Ser Val Ala Ala Ala Ala Leu Leu Glu Glu Arg Ala Gly	
65 70 75 80	
cgg ctc gat gtg ctg gtt aat aac gcc ggc atc gcc ggg gca tgg ccg	288
Arg Leu Asp Val Leu Val Asn Asn Ala Gly Ile Ala Gly Ala Trp Pro	
85 90 95	
gag gag ccc tcg acc gtc aca ccg gcg agc ctc cgg gcg gtg gtg gag	336
Glu Glu Pro Ser Thr Val Thr Pro Ala Ser Leu Arg Ala Val Val Glu	
100 105 110	
acc aac gtg atc ggc gtc gtt cgg gtt acc aac gct atg ctg ccg ttg	384
Thr Asn Val Ile Gly Val Val Arg Val Thr Asn Ala Met Leu Pro Leu	
115 120 125	
cta cgc cgc tcc gag cgc ccg cgg atc gtc aac cag tcc agc cac gtc	432
Leu Arg Arg Ser Glu Arg Pro Arg Ile Val Asn Gln Ser Ser His Val	
130 135 140	
gct tcc ctg acc ttg caa acc acg ccg ggc gtc gac ctc ggc ggg atc	480
Ala Ser Leu Thr Leu Gln Thr Thr Pro Gly Val Asp Leu Gly Gly Ile	
145 150 155 160	
agc gga gcc tac tca ccg tcg aag acg ttc ctc aac gcg atc acc atc	528
Ser Gly Ala Tyr Ser Pro Ser Lys Thr Phe Leu Asn Ala Ile Thr Ile	
165 170 175	
cag tac gcc aag gaa ctc agc gat acc aac atc aaa atc aac aac gcc	576
Gln Tyr Ala Lys Glu Leu Ser Asp Thr Asn Ile Lys Ile Asn Asn Ala	
180 185 190	
tgc ccc ggc tac gtc gcg acc gac ctt aac ggc ttc cac gga acc agc	624
Cys Pro Gly Tyr Val Ala Thr Asp Leu Asn Gly Phe His Gly Thr Ser	
195 200 205	
acg ccg gca gac ggt gcc agg atc gcc att cgg ctc gcc acg ctg cca	672
Thr Pro Ala Asp Gly Ala Arg Ile Ala Ile Arg Leu Ala Thr Leu Pro	
210 215 220	
gac gac ggc ccg acc gga ggc atg ttc gac gac gcc ggg aat gtg ccc	720
Asp Asp Gly Pro Thr Gly Gly Met Phe Asp Asp Ala Gly Asn Val Pro	
225 230 235 240	

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tgg tga
Trp

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<210> 38
<211> 241
<212> PRT
<213> Saccharopolyspora spinosa

<400> 38
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Gly Tyr Glu Ile Ala Ala Gly Leu Gly Ala Leu Gly Trp Ser Val Gly
20 25 30
Ile Gly Ala Arg Asp His Gln Arg Gly Glu Asp Ala Val Ala Lys Leu
35 40 45
Arg Ala Asp Gly Val Asp Ala Phe Ala Val Ser Leu Asp Val Thr Asp
50 55 60
Asp Ala Ser Val Ala Ala Ala Ala Leu Leu Glu Glu Arg Ala Gly
65 70 75 80
Arg Leu Asp Val Leu Val Asn Asn Ala Gly Ile Ala Gly Ala Trp Pro
85 90 95
Glu Glu Pro Ser Thr Val Thr Pro Ala Ser Leu Arg Ala Val Val Glu
100 105 110
Thr Asn Val Ile Gly Val Val Arg Val Thr Asn Ala Met Leu Pro Leu
115 120 125
Leu Arg Arg Ser Glu Arg Pro Arg Ile Val Asn Gln Ser Ser His Val
130 135 140
Ala Ser Leu Thr Leu Gln Thr Thr Pro Gly Val Asp Leu Gly Gly Ile
145 150 155 160
Ser Gly Ala Tyr Ser Pro Ser Lys Thr Phe Leu Asn Ala Ile Thr Ile
165 170 175
Gln Tyr Ala Lys Glu Leu Ser Asp Thr Asn Ile Lys Ile Asn Asn Ala
180 185 190
Cys Pro Gly Tyr Val Ala Thr Asp Leu Asn Gly Phe His Gly Thr Ser
195 200 205

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Thr Pro Ala Asp Gly Ala Arg Ile Ala Ile Arg Leu Ala Thr Leu Pro
 210 215 220

Asp Asp Gly Pro Thr Gly Gly Met Phe Asp Asp Ala Gly Asn Val Pro
 225 230 235 240

Trp

<210> 39

<211> 837

<212> DNA

<213> Saccharopolyspora spinosa

<220>

<221> CDS

<222> (1)..(834)

<223> ORF17; Transkriptions-Regulator

<400> 39

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 Met Glu Thr Arg Glu Leu Arg Tyr Phe Val Ala Val Ala Glu Glu Leu
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cac ttc ggc cgg gcc gcc cag cgc ctg ggc atc gcc cag ccg ccg ctg 96
 His Phe Gly Arg Ala Ala Gln Arg Leu Gly Ile Ala Gln Pro Pro Leu
 20 25 30

tcg cgg acg atc gcc cag ctc gag caa cga ctc gga gtc gtg ttg ctg 144
 Ser Arg Thr Ile Ala Gln Leu Glu Gln Arg Leu Gly Val Val Leu Leu
 35 40 45

caa cgc acc agc cgc aaa gtc tcg ctc acc gaa gcc ggg gca atg ctg 192
 Gln Arg Thr Ser Arg Lys Val Ser Leu Thr Glu Ala Gly Ala Met Leu
 50 55 60

ctg acc gaa ggc cgg gcg atc ctc ggc gcg ctg gca gca gcc gag cga 240
 Leu Thr Glu Gly Arg Ala Ile Leu Gly Ala Leu Ala Ala Ala Glu Arg
 65 70 75 80

cgc acc cag cgt gcc gcg acg agc cag ccc tcg cta gtc ctg gct gcc 288
 Arg Thr Gln Arg Ala Ala Thr Ser Gln Pro Ser Leu Val Leu Ala Ala
 85 90 95

aag gcc ggc gcc tcc ggt gag ctg ctg gcg aag ttg ctc gac gcg tac 336

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Lys Ala Gly Ala Ser Gly Glu Leu Leu Ala Lys Leu Leu Asp Ala Tyr
 100 105 110

gcc gcc gag ccg gga gcc gtg gcc gtc gac ctg ctg ctc tgc gaa tcc 384
 Ala Ala Glu Pro Gly Ala Val Ala Val Asp Leu Leu Leu Cys Glu Ser
 115 120 125

cag ccc cag aaa acg ctg cat gac ggc cgg gcc gac gtg gcg ctg ttg 432
 Gln Pro Gln Lys Thr Leu His Asp Gly Arg Ala Asp Val Ala Leu Leu
 130 135 140

cat caa ccc ttc gac ccg acg gcc gaa ctc gac atc gaa att ctg aac 480
 His Gln Pro Phe Asp Pro Thr Ala Glu Leu Asp Ile Glu Ile Leu Asn
 145 150 155 160

acc gag caa caa gtc gcc att ctt ccg acc tcg cat ccg ctt gcc agc 528
 Thr Glu Gln Gln Val Ala Ile Leu Pro Thr Ser His Pro Leu Ala Ser
 165 170 175

gag ccc cat gta cgg atg gcg gat gtc agc tca ctg ccg gat ctc ccg 576
 Glu Pro His Val Arg Met Ala Asp Val Ser Ser Leu Pro Asp Leu Pro
 180 185 190

ctt gcg cgc tgg ccc ggc ccc gac ggc gtc tat cca gat ggc ccc ggc 624
 Leu Ala Arg Trp Pro Gly Pro Asp Gly Val Tyr Pro Asp Gly Pro Gly
 195 200 205

gtg gaa gta cgc aac cag acg caa ctg ttc caa atg atc gca ctc ggc 672
 Val Glu Val Arg Asn Gln Thr Gln Leu Phe Gln Met Ile Ala Leu Gly
 210 215 220

cgc act acc gtg gtc atg ccc gaa tcc agt cgc gtc aac ctg ctc gaa 720
 Arg Thr Thr Val Val Met Pro Glu Ser Ser Arg Val Asn Leu Leu Glu
 225 230 235 240

ggc ctc gcc gcc gta ccg gtt cta gac gcg ccg gac gtg acg aca gtc 768
 Gly Leu Ala Ala Val Pro Val Leu Asp Ala Pro Asp Val Thr Thr Val
 245 250 255

atc gcc tgg ccg ccc cac agc cgc tcc cga gca ctc gcc ggc ttg gtc 816
 Ile Ala Trp Pro Pro His Ser Arg Ser Arg Ala Leu Ala Gly Leu Val
 260 265 270

cgc gtg gcc aca ctc ctc taa 837
 Arg Val Ala Thr Leu Leu
 275

<210> 40

<211> 278

<212> PRT

<213> Saccharopolyspora spinosa

<400> 40

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 1 5 10 15

His Phe Gly Arg Ala Ala Gln Arg Leu Gly Ile Ala Gln Pro Pro Leu
 20 25 30

Ser Arg Thr Ile Ala Gln Leu Glu Gln Arg Leu Gly Val Val Leu Leu
 35 40 45

Gln Arg Thr Ser Arg Lys Val Ser Leu Thr Glu Ala Gly Ala Met Leu
 50 55 60

Leu Thr Glu Gly Arg Ala Ile Leu Gly Ala Leu Ala Ala Ala Glu Arg
 65 70 75 80

Arg Thr Gln Arg Ala Ala Thr Ser Gln Pro Ser Leu Val Leu Ala Ala
 85 90 95

Lys Ala Gly Ala Ser Gly Glu Leu Leu Ala Lys Leu Leu Asp Ala Tyr
 100 105 110

Ala Ala Glu Pro Gly Ala Val Ala Val Asp Leu Leu Leu Cys Glu Ser
 115 120 125

Gln Pro Gln Lys Thr Leu His Asp Gly Arg Ala Asp Val Ala Leu Leu
 130 135 140

His Gln Pro Phe Asp Pro Thr Ala Glu Leu Asp Ile Glu Ile Leu Asn
 145 150 155 160

Thr Glu Gln Gln Val Ala Ile Leu Pro Thr Ser His Pro Leu Ala Ser
 165 170 175

Glu Pro His Val Arg Met Ala Asp Val Ser Ser Leu Pro Asp Leu Pro
 180 185 190

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820 825 830

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Ala Met Pro Glu Ser Asp Val Ser Thr Ala Leu Arg Glu Lys Leu Arg
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Cys Ala Gly Gly Phe Leu Gln Gly Val Ser Glu Phe Asp Ala Gly Phe			
	100	105	110
ttc ggg att tcg ccg cgt gag gcg ctg gcg atg gat ccg cag cag cgg			384
Phe Gly Ile Ser Pro Arg Glu Ala Leu Ala Met Asp Pro Gln Gln Arg			
	115	120	125
ttg ctg ctg gaa gtc gcg tgg gag gtc ttc gag cgg gct ggg ctg gag			432
Leu Leu Leu Glu Val Ala Trp Glu Val Phe Glu Arg Ala Gly Leu Glu			
	130	135	140
cag cgg tcg aca cgc ggt tcc cgc gtt ggc gtg ttc gtc ggc acc aat			480
Gln Arg Ser Thr Arg Gly Ser Arg Val Gly Val Phe Val Gly Thr Asn			
	145	150	155
ggc cag gac tac gcg tcg tgg ttg cgg acg ccg ccg cct gcg gtg gca			528
Gly Gln Asp Tyr Ala Ser Trp Leu Arg Thr Pro Pro Pro Ala Val Ala			
	165	170	175
ggt cat gtg ctg acg ggc ggt gcg gca gcg gtt ctt tcg ggc cgg gtt			576
Gly His Val Leu Thr Gly Gly Ala Ala Ala Val Leu Ser Gly Arg Val			
	180	185	190
gcg tat tcg ttc ggg ttc gag ggt cct gcg gtg acg gtg gat acg gcg			624
Ala Tyr Ser Phe Gly Phe Glu Gly Pro Ala Val Thr Val Asp Thr Ala			
	195	200	205
tgt tcg tcg tcg ttg gtg gcg ttg cac ctg gcg ggg caa gca ctg cgg			672
Cys Ser Ser Ser Leu Val Ala Leu His Leu Ala Gly Gln Ala Leu Arg			
	210	215	220
gcc ggt gag tgc gac ctt gcc ctt gcc ggt ggc gtc acg gtg atg tcg			720
Ala Gly Glu Cys Asp Leu Ala Leu Ala Gly Gly Val Thr Val Met Ser			
	225	230	235
acg ccg aag gtg ttc ctg gag ttc tcc cgc caa cgg ggt ctc gcg ccg			768
Thr Pro Lys Val Phe Leu Glu Phe Ser Arg Gln Arg Gly Leu Ala Pro			

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245	250	255	
gat ggg cgg tgc aag tcg ttc gcg gcg ggt gcg gat ggc act gga tgg			816
Asp Gly Arg Cys Lys Ser Phe Ala Ala Gly Ala Asp Gly Thr Gly Trp			
260	265	270	
ggt gag ggt gcc gga ctg ttg ttg ctg gag cgg ttg tcg gat gcc cgg			864
Gly Glu Gly Ala Gly Leu Leu Leu Leu Glu Arg Leu Ser Asp Ala Arg			
275	280	285	
cgg aat ggg cat gag gtg ctg gcg gtt gtt cgt ggt agt gcg gtg aat			912
Arg Asn Gly His Glu Val Leu Ala Val Val Arg Gly Ser Ala Val Asn			
290	295	300	
cag gac ggt gcg tcg aat ggt ttg acc gcg ccg aat ggt tcg tcg cag			960
Gln Asp Gly Ala Ser Asn Gly Leu Thr Ala Pro Asn Gly Ser Ser Gln			
305	310	315	320
cag cgg gtg att acc cag gcg ttg gcg agt gcg ggg ttg tcg gtg tcc			1008
Gln Arg Val Ile Thr Gln Ala Leu Ala Ser Ala Gly Leu Ser Val Ser			
325	330	335	
gat gtg gat gct gtg gag gcg cat ggg acg ggc acg cgg ctt ggt gat			1056
Asp Val Asp Ala Val Glu Ala His Gly Thr Gly Thr Arg Leu Gly Asp			
340	345	350	
ccg atc gag gcg cag gcg ctg atc gcc acc tac ggc cgt gat cgt gat			1104
Pro Ile Glu Ala Gln Ala Leu Ile Ala Thr Tyr Gly Arg Asp Arg Asp			
355	360	365	
cct ggc cgg ccg ttg tgg ttg ggg tcg gtc aag tcg aac atc ggt cat			1152
Pro Gly Arg Pro Leu Trp Leu Gly Ser Val Lys Ser Asn Ile Gly His			
370	375	380	
acg caa gcg gcg gcg ggt gtg gct ggt gtg atc aag atg gtg atg gcg			1200
Thr Gln Ala Ala Ala Gly Val Ala Gly Val Ile Lys Met Val Met Ala			
385	390	395	400
atg cgg cac ggg cag ctg cca cgc acg ttg cac gtg gaa tcg ccg tcg			1248
Met Arg His Gly Gln Leu Pro Arg Thr Leu His Val Glu Ser Pro Ser			
405	410	415	
ccg gag gtg gat tgg tcg gcg ggg acg gtt caa ctc ctt acg gag aac			1296
Pro Glu Val Asp Trp Ser Ala Gly Thr Val Gln Leu Leu Thr Glu Asn			
420	425	430	
acg ccc tgg ccc agg agt ggt cgt gtt cgt cgg gtg ggg gtg tcg tcg			1344
Thr Pro Trp Pro Arg Ser Gly Arg Val Arg Arg Val Gly Val Ser Ser			

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435	440	445	
ttc ggg atc agt ggt act aac gcg cac gtc atc ctc gaa cag ccc ccg			1392
Phe Gly Ile Ser Gly Thr Asn Ala His Val Ile Leu Glu Gln Pro Pro			
450	455	460	
gga gtg ccg agt cag tct gcg ggg ccg ggt tcg ggt tct gtc gtg gat			1440
Gly Val Pro Ser Gln Ser Ala Gly Pro Gly Ser Gly Ser Val Val Asp			
465	470	475	480
gtt ccg gtg gtg ccg tgg atg gtg tcg ggc aaa aca ccc gaa gcg cta			1488
Val Pro Val Val Pro Trp Met Val Ser Gly Lys Thr Pro Glu Ala Leu			
	485	490	495
tcc gcg cag gca acg gcg ttg atg acc tat ctg gac gag cga cct gat			1536
Ser Ala Gln Ala Thr Ala Leu Met Thr Tyr Leu Asp Glu Arg Pro Asp			
	500	505	510
gtc tcc tcg ctg gat gtt ggg tac tcg ctg gcg ttg aca cgg tcg gcg			1584
Val Ser Ser Leu Asp Val Gly Tyr Ser Leu Ala Leu Thr Arg Ser Ala			
	515	520	525
ctg gat gag cga gcg gtg gtg ctg ggg tcg gac cgt gaa acg ttg ttg			1632
Leu Asp Glu Arg Ala Val Val Leu Gly Ser Asp Arg Glu Thr Leu Leu			
	530	535	540
tgc ggt gtg aaa gcg ctg tct gcc ggt cat gag gct tct ggg ttg gtg			1680
Cys Gly Val Lys Ala Leu Ser Ala Gly His Glu Ala Ser Gly Leu Val			
545	550	555	560
acc gga tct gtg ggg gct ggg ggc cgc atc ggg ttt gtg ttt tcc ggt			1728
Thr Gly Ser Val Gly Ala Gly Gly Arg Ile Gly Phe Val Phe Ser Gly			
	565	570	575
cag ggt ggt cag tgg ctg ggg atg ggc cgg ggg ctt tac cgg gct ttt			1776
Gln Gly Gly Gln Trp Leu Gly Met Gly Arg Gly Leu Tyr Arg Ala Phe			
	580	585	590
ccg gtg ttc gct gct gcc ttt gac gaa gct tgt gcc gag ctg gat gca			1824
Pro Val Phe Ala Ala Ala Phe Asp Glu Ala Cys Ala Glu Leu Asp Ala			
	595	600	605
cat ctg ggc cag gaa atc ggg gtt cgg gag gtg gtg tcc ggt tcg gat			1872
His Leu Gly Gln Glu Ile Gly Val Arg Glu Val Val Ser Gly Ser Asp			
	610	615	620
gcg cag ttg ctg gat cgg acg ttg tgg gcg cag tcg ggt ttg ttc gcg			1920
Ala Gln Leu Leu Asp Arg Thr Leu Trp Ala Gln Ser Gly Leu Phe Ala			

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625	630	635	640	
ttg cag gtg ggc ttg ctg aag ttg ctg gat tcg tgg ggg gtt cgg ccg				1968
Leu Gln Val Gly Leu Leu Lys Leu Leu Asp Ser Trp Gly Val Arg Pro				
645		650	655	
agt gtg gtg ttg ggg cat tcg gtg ggc gag ttg gcg gcg gcg ttc gcg				2016
Ser Val Val Leu Gly His Ser Val Gly Glu Leu Ala Ala Ala Phe Ala				
660		665	670	
gcg ggt gtg gtg tcg ttg tcg ggt gcg gct cgg ttg gtg gcg ggt cgt				2064
Ala Gly Val Val Ser Leu Ser Gly Ala Ala Arg Leu Val Ala Gly Arg				
675		680	685	
gcc cgg ttg atg cag gcg ttg ccg tct ggc ggt ggg atg ctg gcg gtg				2112
Ala Arg Leu Met Gln Ala Leu Pro Ser Gly Gly Gly Met Leu Ala Val				
690		695	700	
cct gct ggt gag gag ctg ttg tgg tcg ttg ttg gcc gat cag ggt gat				2160
Pro Ala Gly Glu Glu Leu Leu Trp Ser Leu Leu Ala Asp Gln Gly Asp				
705		710	715	720
cgt gtg ggg atc gcc gcg gtc aac gct gcg ggg tcg gtg gtg ctc tct				2208
Arg Val Gly Ile Ala Ala Val Asn Ala Ala Gly Ser Val Val Leu Ser				
725		730	735	
ggt gat cgg gat gtg ctc gat gac ctt gcc ggt cgg ctg gac ggg caa				2256
Gly Asp Arg Asp Val Leu Asp Asp Leu Ala Gly Arg Leu Asp Gly Gln				
740		745	750	
ggg atc cgg tcg agg tgg ttg cgg gtg tcg cat gcg ttt cat tcg tat				2304
Gly Ile Arg Ser Arg Trp Leu Arg Val Ser His Ala Phe His Ser Tyr				
755		760	765	
cgg atg gat ccg atg ctg gcg gag ttc gcc gaa ttg gca cga acc gtg				2352
Arg Met Asp Pro Met Leu Ala Glu Phe Ala Glu Leu Ala Arg Thr Val				
770		775	780	
gat tac cgg cgt tgt gaa gtg ccg atc gtg tcg acc ttg acc gga gac				2400
Asp Tyr Arg Arg Cys Glu Val Pro Ile Val Ser Thr Leu Thr Gly Asp				
785		790	795	800
ctc gat gac gct ggc agg atg agc ggg ccc gac tac tgg gtg cgt cag				2448
Leu Asp Asp Ala Gly Arg Met Ser Gly Pro Asp Tyr Trp Val Arg Gln				
805		810	815	
gtg cga gag ccg gtc cgc ttc gcc gac ggt gtc cag gcg ctg gtc gag				2496
Val Arg Glu Pro Val Arg Phe Ala Asp Gly Val Gln Ala Leu Val Glu				

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820	825	830	
cac gat gtg gcc act gtt gtc gag ctc ggt ccg gac ggg gcg ttg tcg			2544
His Asp Val Ala Thr Val Val Glu Leu Gly Pro Asp Gly Ala Leu Ser			
835	840	845	
gcg ctg atc cag gaa tgt gtc gcc gca tcc gat cac gcc ggg cgg ctg			2592
Ala Leu Ile Gln Glu Cys Val Ala Ala Ser Asp His Ala Gly Arg Leu			
850	855	860	
agc gcg gtc ccg gcg atg cgc agg aac cag gac gag gcg cag aag gtg			2640
Ser Ala Val Pro Ala Met Arg Arg Asn Gln Asp Glu Ala Gln Lys Val			
865	870	875	880
atg acg gcc ctg gca cac gtc cac gta cgt ggt ggt gcg gtg gac tgg			2688
Met Thr Ala Leu Ala His Val His Val Arg Gly Gly Ala Val Asp Trp			
885	890	895	
cgg tcg ttc ttc gcc ggt acg gga gcg aaa caa atc gag ctg ccc acc			2736
Arg Ser Phe Phe Ala Gly Thr Gly Ala Lys Gln Ile Glu Leu Pro Thr			
900	905	910	
tac gcc ttc caa cga cag cgg tac tgg ctg gtg cca tcg gat tcc ggt			2784
Tyr Ala Phe Gln Arg Gln Arg Tyr Trp Leu Val Pro Ser Asp Ser Gly			
915	920	925	
gat gtg aca ggt gcc ggt ctg gcc ggg gcg gag cat ccg ctg ttg ggt			2832
Asp Val Thr Gly Ala Gly Leu Ala Gly Ala Glu His Pro Leu Leu Gly			
930	935	940	
gct gtg gtg ccg gtc gcg ggt ggt gac gag gtg ttg ctg acc ggc agg			2880
Ala Val Val Pro Val Ala Gly Gly Asp Glu Val Leu Leu Thr Gly Arg			
945	950	955	960
att tcg gtg cgg acg cat ccg tgg ctg gcc gaa cac cgg gtg ctg ggt			2928
Ile Ser Val Arg Thr His Pro Trp Leu Ala Glu His Arg Val Leu Gly			
965	970	975	
gaa gtg atc gtt gcg ggc acc gcg ttg ctg gag atc gcc ttg cac gcg			2976
Glu Val Ile Val Ala Gly Thr Ala Leu Leu Glu Ile Ala Leu His Ala			
980	985	990	
ggg gaa cgt ctt ggt tgt gaa cgg gtg gaa gag ctc acc ctg gaa gca			3024
Gly Glu Arg Leu Gly Cys Glu Arg Val Glu Glu Leu Thr Leu Glu Ala			
995	1000	1005	
ccg ctg gtc ctg ccg gag cgc ggg gcg atc cag gtt cag ctg cga gtg			3072
Pro Leu Val Leu Pro Glu Arg Gly Ala Ile Gln Val Gln Leu Arg Val			

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1010	1015	1020	
ggc gcg ccc gag aat tcc gga cgc agg ccg atg gcg ctg tat tca cgc			3120
Gly Ala Pro Glu Asn Ser Gly Arg Arg Pro Met Ala Leu Tyr Ser Arg			
1025	1030	1035	1040
ccc gaa ggg gcg gcg gag cat gac tgg acg cgg cac gcc acg ggc cgg			3168
Pro Glu Gly Ala Ala Glu His Asp Trp Thr Arg His Ala Thr Gly Arg			
1045	1050	1055	
ttg gcg cca ggc cgc ggc gag gcg gct gga gac ctg gcc gac tgg ccg			3216
Leu Ala Pro Gly Arg Gly Glu Ala Ala Gly Asp Leu Ala Asp Trp Pro			
1060	1065	1070	
gct cct ggc gcg ctg ccg gtc gac ctc gac gaa ttc tat cgg gac ctc			3264
Ala Pro Gly Ala Leu Pro Val Asp Leu Asp Glu Phe Tyr Arg Asp Leu			
1075	1080	1085	
gca gag ctt ggg ctg gag tac ggc ccg atc ttc caa ggg ctc aag gcg			3312
Ala Glu Leu Gly Leu Glu Tyr Gly Pro Ile Phe Gln Gly Leu Lys Ala			
1090	1095	1100	
gcc tgg cgg caa ggg gac gag gtg tac gcc gaa gcc gcg ctg ccg gga			3360
Ala Trp Arg Gln Gly Asp Glu Val Tyr Ala Glu Ala Ala Leu Pro Gly			
1105	1110	1115	1120
acg gaa gat tct ggt ttc ggg gtg cat ccg gca ctg ctg gac gcg gct			3408
Thr Glu Asp Ser Gly Phe Gly Val His Pro Ala Leu Leu Asp Ala Ala			
1125	1130	1135	
ctg cac gca acg gct gtc cga gac atg gat gac gca cgc ttg ccg ttc			3456
Leu His Ala Thr Ala Val Arg Asp Met Asp Asp Ala Arg Leu Pro Phe			
1140	1145	1150	
cag tgg gaa ggt gtg tcc ctg cac gcc aag gcc gcg ccg gct ttg cgg			3504
Gln Trp Glu Gly Val Ser Leu His Ala Lys Ala Ala Pro Ala Leu Arg			
1155	1160	1165	
gtc cgc gtg gtc ccg gct ggt gac gat gcc aag tcc ctg ctg gtt tgt			3552
Val Arg Val Val Pro Ala Gly Asp Asp Ala Lys Ser Leu Leu Val Cys			
1170	1175	1180	
gat ggc acc ggt cga ccg gtg atc tcg gtg gac cga ctc gta ttg cgg			3600
Asp Gly Thr Gly Arg Pro Val Ile Ser Val Asp Arg Leu Val Leu Arg			
1185	1190	1195	1200
tcg gct gcg gcc cgg cgg acc ggt gcg cgc cga cag gcc cat caa gct			3648
Ser Ala Ala Ala Arg Arg Thr Gly Ala Arg Arg Gln Ala His Gln Ala			

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1205	1210	1215	
cgg ttg tac cgg ttg agc tgg cca acg gtt caa ctg ccg aca tcc gct			3696
Arg Leu Tyr Arg Leu Ser Trp Pro Thr Val Gln Leu Pro Thr Ser Ala			
1220	1225	1230	
cag cca ccg tcc tgc gtg ctt ctc ggc acc tca gaa gtg tcc gct gac			3744
Gln Pro Pro Ser Cys Val Leu Leu Gly Thr Ser Glu Val Ser Ala Asp			
1235	1240	1245	
ata cag gtg tat ccg gac ctc cgg tcg ttg acg gct gcg ttg gat gcc			3792
Ile Gln Val Tyr Pro Asp Leu Arg Ser Leu Thr Ala Ala Leu Asp Ala			
1250	1255	1260	
ggt gcc gaa cca ccc ggc gtc gtc atc gca ccc acg ccc ccc ggc ggt			3840
Gly Ala Glu Pro Pro Gly Val Val Ile Ala Pro Thr Pro Pro Gly Gly			
1265	1270	1275	1280
gga cga aca gcg gat gtc cgg gag acg act cgg cat gca ctc gac ctg			3888
Gly Arg Thr Ala Asp Val Arg Glu Thr Thr Arg His Ala Leu Asp Leu			
1285	1290	1295	
gta caa ggc tgg ctt tcc gat cag cga ctc aac gaa tcc cga ttg ctc			3936
Val Gln Gly Trp Leu Ser Asp Gln Arg Leu Asn Glu Ser Arg Leu Leu			
1300	1305	1310	
ctg gtg aca cag gga gca gtg gcc gtg gag ccg ggc gaa ccc gtg acc			3984
Leu Val Thr Gln Gly Ala Val Ala Val Glu Pro Gly Glu Pro Val Thr			
1315	1320	1325	
gat ctg gcg cag gcc gcg ctc tgg gga ctg ctg cgg tcg acg cag acc			4032
Asp Leu Ala Gln Ala Ala Leu Trp Gly Leu Leu Arg Ser Thr Gln Thr			
1330	1335	1340	
gaa cac cct gat cgc ttc gtc ctc gtc gat gtg cct gag ccc gcg caa			4080
Glu His Pro Asp Arg Phe Val Leu Val Asp Val Pro Glu Pro Ala Gln			
1345	1350	1355	1360
ctc ctc ccc gcg ctg ccg ggg gtg ctg gcc tgc ggc gaa cct cag ctc			4128
Leu Leu Pro Ala Leu Pro Gly Val Leu Ala Cys Gly Glu Pro Gln Leu			
1365	1370	1375	
gcg ttg cga cgt ggc ggc gct cat gcg ccc aga ctg gct gga ctg ggc			4176
Ala Leu Arg Arg Gly Gly Ala His Ala Pro Arg Leu Ala Gly Leu Gly			
1380	1385	1390	
agc gat gac gtc ctg ccc gtg ccg gac ggc acc ggg tgg cga ttg gag			4224
Ser Asp Asp Val Leu Pro Val Pro Asp Gly Thr Gly Trp Arg Leu Glu			

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1395	1400	1405	
gcc acg cgc ccg gga agc ctg gat ggg ttg gca ttg gtg gac gaa ccg			4272
Ala Thr Arg Pro Gly Ser Leu Asp Gly Leu Ala Leu Val Asp Glu Pro			
1410	1415	1420	
acg gcc acg gca ccg ctg ggt gac ggt gag gtc agg att gcg atg cgc			4320
Thr Ala Thr Ala Pro Leu Gly Asp Gly Glu Val Arg Ile Ala Met Arg			
1425	1430	1435	1440
gcg gcc ggg gtg aac ttc cgg gat gcg ctc atc gcg ctc ggt atg tat			4368
Ala Ala Gly Val Asn Phe Arg Asp Ala Leu Ile Ala Leu Gly Met Tyr			
1445	1450	1455	
ccc ggt gtg gca tcg ctg ggc agt gag ggc gcc ggg gtc gtg gtg gag			4416
Pro Gly Val Ala Ser Leu Gly Ser Glu Gly Ala Gly Val Val Val Glu			
1460	1465	1470	
acc ggc ccc ggc gtc acc ggc ctg gca ccc ggc gac cgc gtg atg gga			4464
Thr Gly Pro Gly Val Thr Gly Leu Ala Pro Gly Asp Arg Val Met Gly			
1475	1480	1485	
atg atc ccg aag gcg ttc ggg ccg ctc gcg gtc gcc gac cat cgc atg			4512
Met Ile Pro Lys Ala Phe Gly Pro Leu Ala Val Ala Asp His Arg Met			
1490	1495	1500	
gtg acg agg att ccc gct ggt tgg agc ttc gcg cgg gcc gca tcg gtg			4560
Val Thr Arg Ile Pro Ala Gly Trp Ser Phe Ala Arg Ala Ala Ser Val			
1505	1510	1515	1520
ccg atc gtc ttt ctc acc gcc tac tac gcg ctg gtt gat ctc gcc ggg			4608
Pro Ile Val Phe Leu Thr Ala Tyr Tyr Ala Leu Val Asp Leu Ala Gly			
1525	1530	1535	
ttg aga cca ggg gag tcg ttg ctg gtt cat tcg gcc gcc ggt ggg gtg			4656
Leu Arg Pro Gly Glu Ser Leu Leu Val His Ser Ala Ala Gly Gly Val			
1540	1545	1550	
ggg atg gcc gcg atc caa ctc gcc agg cac ctc ggt gca gag gtg tac			4704
Gly Met Ala Ala Ile Gln Leu Ala Arg His Leu Gly Ala Glu Val Tyr			
1555	1560	1565	
gcc acc gct agc gag gac aag tgg caa gcc gtg gag ctg agc cga gaa			4752
Ala Thr Ala Ser Glu Asp Lys Trp Gln Ala Val Glu Leu Ser Arg Glu			
1570	1575	1580	
cac ctc gct tcg tcg cgg acg tgc gat ttc gag cag cag ttc ctc ggg			4800
His Leu Ala Ser Ser Arg Thr Cys Asp Phe Glu Gln Gln Phe Leu Gly			

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1585	1590	1595	1600	
gca acc ggc gga cgc ggc gtc gac gtc gtg ctc aac tcc ctc gcc ggg				4848
Ala Thr Gly Gly Arg Gly Val Asp Val Val Leu Asn Ser Leu Ala Gly				
	1605	1610	1615	
gag ttc gcc gat gcg tct ctg cga atg ctg ccg cgc ggt ggc cgt ttc				4896
Glu Phe Ala Asp Ala Ser Leu Arg Met Leu Pro Arg Gly Gly Arg Phe				
	1620	1625	1630	
ctg gag ttg ggg aag acg gat gtt cgt gac ccc gtc gag gtc gcc gat				4944
Leu Glu Leu Gly Lys Thr Asp Val Arg Asp Pro Val Glu Val Ala Asp				
	1635	1640	1645	
gcg cat ccg ggc gtg tct tac cag gct ttc gat acc gta gag gca ggc				4992
Ala His Pro Gly Val Ser Tyr Gln Ala Phe Asp Thr Val Glu Ala Gly				
	1650	1655	1660	
ccg cag cga atc ggc gag atg ctt cac gag ctg gtg gag ttg ttc gag				5040
Pro Gln Arg Ile Gly Glu Met Leu His Glu Leu Val Glu Leu Phe Glu				
	1665	1670	1675	1680
gga cgc gtg ctg gag ccc ctg cct gtc acg gct tgg gac gtt cgg cag				5088
Gly Arg Val Leu Glu Pro Leu Pro Val Thr Ala Trp Asp Val Arg Gln				
	1685	1690	1695	
gcg ccc gag gcg cta cgg cac ctg agc caa gcg cgg cat gtg gga aag				5136
Ala Pro Glu Ala Leu Arg His Leu Ser Gln Ala Arg His Val Gly Lys				
	1700	1705	1710	
ctg gtg ctc acc atg cct ccg gtg tgg gac gcc gca ggc acg gtt ctg				5184
Leu Val Leu Thr Met Pro Pro Val Trp Asp Ala Ala Gly Thr Val Leu				
	1715	1720	1725	
gtt acc ggc gga acg gga gca ctt ggc gca gag gtc gcc cgg cac ctc				5232
Val Thr Gly Gly Thr Gly Ala Leu Gly Ala Glu Val Ala Arg His Leu				
	1730	1735	1740	
gtg atc gag cgc ggg gtg cga aac ctg gtc ctc gtc agc agg cgc ggt				5280
Val Ile Glu Arg Gly Val Arg Asn Leu Val Leu Val Ser Arg Arg Gly				
	1745	1750	1755	1760
ccc gca gcc agt ggc gct gct gag ctc gtg gcg caa ctg acg gcc tac				5328
Pro Ala Ala Ser Gly Ala Ala Glu Leu Val Ala Gln Leu Thr Ala Tyr				
	1765	1770	1775	
ggt gcc gag gtt tcc ttg cag gct tgc gat gtc gcc gat cgt gag acc				5376
Gly Ala Glu Val Ser Leu Gln Ala Cys Asp Val Ala Asp Arg Glu Thr				

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1780	1785	1790	
ttg gcg aag gtg ctt gcc agc atc ccg gac gag cat ccg ttg acc gcc			5424
Leu Ala Lys Val Leu Ala Ser Ile Pro Asp Glu His Pro Leu Thr Ala			
1795	1800	1805	
gtg gtg cac gcg gct ggt gtt ctc gac gac gga gtg tcc gaa tcg ctc			5472
Val Val His Ala Ala Gly Val Leu Asp Asp Gly Val Ser Glu Ser Leu			
1810	1815	1820	
acc gtg gag cgg ctg gac cag gtt ctg cgc ccg aag gtc gat ggc gcg			5520
Thr Val Glu Arg Leu Asp Gln Val Leu Arg Pro Lys Val Asp Gly Ala			
1825	1830	1835	1840
cgg aat ctg ctc gag ctg atc gac ccg gac gtg gcc ctc gtg ttg ttc			5568
Arg Asn Leu Leu Glu Leu Ile Asp Pro Asp Val Ala Leu Val Leu Phe			
1845	1850	1855	
tcg tcg gtg tcg ggt gtg ctc ggc agc ggt ggg cag ggt aac tac gcg			5616
Ser Ser Val Ser Gly Val Leu Gly Ser Gly Gly Gln Gly Asn Tyr Ala			
1860	1865	1870	
gcg gcc aac tcc ttc ctc gac gca ttg gcg cag caa agg cag tcg cgc			5664
Ala Ala Asn Ser Phe Leu Asp Ala Leu Ala Gln Gln Arg Gln Ser Arg			
1875	1880	1885	
ggc cta ccg acg aga tca ttg gcc tgg ggg ccc tgg gcg gaa cat ggc			5712
Gly Leu Pro Thr Arg Ser Leu Ala Trp Gly Pro Trp Ala Glu His Gly			
1890	1895	1900	
atg gcc agc acc ttg cgc gaa gcc gag cag gat cga ttg gcg cga tct			5760
Met Ala Ser Thr Leu Arg Glu Ala Glu Gln Asp Arg Leu Ala Arg Ser			
1905	1910	1915	1920
ggg ttg ctg ccg atc tcg acc gag gag ggg ttg tcc cag ttc gac gcc			5808
Gly Leu Leu Pro Ile Ser Thr Glu Glu Gly Leu Ser Gln Phe Asp Ala			
1925	1930	1935	
gcg tgc ggc ggc gcg cat acc gtg gtg gcg ccg gtt cga ttc agc cgc			5856
Ala Cys Gly Gly Ala His Thr Val Val Ala Pro Val Arg Phe Ser Arg			
1940	1945	1950	
ttg tcc gac ggg aac gcg atc aag ttc tcc gtc ctg caa ggt ttg gtc			5904
Leu Ser Asp Gly Asn Ala Ile Lys Phe Ser Val Leu Gln Gly Leu Val			
1955	1960	1965	
ggg ccg cat cgc gtc aac aaa gcg gcg act gcg gat gat gcc gag agc			5952
Gly Pro His Arg Val Asn Lys Ala Ala Thr Ala Asp Asp Ala Glu Ser			

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1970	1975	1980	
ctc cgg aaa cgg ttg gga cgc ttg ccg gat gca gaa caa cat cgg att			6000
Leu Arg Lys Arg Leu Gly Arg Leu Pro Asp Ala Glu Gln His Arg Ile			
1985	1990	1995	2000
ctg ctg gac ctc gtc cgc atg cat gtg gcg gca gtg ctc gga ttc gcc			6048
Leu Leu Asp Leu Val Arg Met His Val Ala Ala Val Leu Gly Phe Ala			
	2005	2010	2015
ggt tct cag gag atc acc gcg gac ggc acg ttc aag gtg ctg ggc ttc			6096
Gly Ser Gln Glu Ile Thr Ala Asp Gly Thr Phe Lys Val Leu Gly Phe			
	2020	2025	2030
gac tcg ttg acc gtg gtc gag ttg cgc aac cgg atc aac ggg gcg acg			6144
Asp Ser Leu Thr Val Val Glu Leu Arg Asn Arg Ile Asn Gly Ala Thr			
	2035	2040	2045
ggg ctg cga ctg ccc gcc acc ctg gtg ttc aac tac ccg acg ccg gat			6192
Gly Leu Arg Leu Pro Ala Thr Leu Val Phe Asn Tyr Pro Thr Pro Asp			
	2050	2055	2060
gcg ctc gcc gcg cac ctc gtc acc gcg ctg tcc gca gac cgc ctg gcc			6240
Ala Leu Ala Ala His Leu Val Thr Ala Leu Ser Ala Asp Arg Leu Ala			
	2065	2070	2075
ggg aca ttc gag gaa ctc gac agg tgg gcg gcg aac ctg ccc acg ctg			6288
Gly Thr Phe Glu Glu Leu Asp Arg Trp Ala Ala Asn Leu Pro Thr Leu			
	2085	2090	2095
gcc agg gat gag gcc acg cgg gcg cag atc acc acc cgg cta cag gcg			6336
Ala Arg Asp Glu Ala Thr Arg Ala Gln Ile Thr Thr Arg Leu Gln Ala			
	2100	2105	2110
atc ttg cag agc ctg gcg gac gtg tcc ggc gga acc ggc ggc ggc tcc			6384
Ile Leu Gln Ser Leu Ala Asp Val Ser Gly Gly Thr Gly Gly Gly Ser			
	2115	2120	2125
gtg ccg gac cgg ctc aga tcg gcc acg gac gac gag ctt ttc caa ctc			6432
Val Pro Asp Arg Leu Arg Ser Ala Thr Asp Asp Glu Leu Phe Gln Leu			
	2130	2135	2140
ctc gac aac gat ctc gaa ctt ccc tga			6459
Leu Asp Asn Asp Leu Glu Leu Pro			
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<212> PRT

<213> Saccharopolyspora spinosa

<400> 44

Met Thr Val Thr Thr Ser Tyr Glu Glu Val Val Glu Ala Leu Arg Ala

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5

10

15

Ser Leu Lys Glu Asn Glu Arg Leu Arg Arg Gly Arg Asp Arg Phe Ser

20

25

30

Ala Glu Lys Asp Asp Pro Ile Ala Ile Val Ala Met Ser Cys Arg Tyr

35

40

45

Pro Gly Gln Val Ser Ser Pro Glu Asp Leu Trp Gln Leu Ala Ala Gly

50

55

60

Gly Val Asp Ala Ile Ser Glu Val Pro Gly Asp Arg Gly Trp Asp Leu

65

70

75

80

Asp Gly Val Phe Val Pro Asp Ser Asp Arg Pro Gly Thr Ser Tyr Ala

85

90

95

Cys Ala Gly Gly Phe Leu Gln Gly Val Ser Glu Phe Asp Ala Gly Phe

100

105

110

Phe Gly Ile Ser Pro Arg Glu Ala Leu Ala Met Asp Pro Gln Gln Arg

115

120

125

Leu Leu Leu Glu Val Ala Trp Glu Val Phe Glu Arg Ala Gly Leu Glu

130

135

140

Gln Arg Ser Thr Arg Gly Ser Arg Val Gly Val Phe Val Gly Thr Asn

145

150

155

160

Gly Gln Asp Tyr Ala Ser Trp Leu Arg Thr Pro Pro Pro Ala Val Ala

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170

175

Gly His Val Leu Thr Gly Gly Ala Ala Ala Val Leu Ser Gly Arg Val

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185

190

Ala Tyr Ser Phe Gly Phe Glu Gly Pro Ala Val Thr Val Asp Thr Ala

195

200

205

Cys Ser Ser Ser Leu Val Ala Leu His Leu Ala Gly Gln Ala Leu Arg

210

215

220

Ala Gly Glu Cys Asp Leu Ala Leu Ala Gly Gly Val Thr Val Met Ser

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Thr Pro Lys Val Phe Leu Glu Phe Ser Arg Gln Arg Gly Leu Ala Pro			
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Asp Gly Arg Cys Lys Ser Phe Ala Ala Gly Ala Asp Gly Thr Gly Trp			
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Gly Glu Gly Ala Gly Leu Leu Leu Leu Glu Arg Leu Ser Asp Ala Arg			
275	280	285	
Arg Asn Gly His Glu Val Leu Ala Val Val Arg Gly Ser Ala Val Asn			
290	295	300	
Gln Asp Gly Ala Ser Asn Gly Leu Thr Ala Pro Asn Gly Ser Ser Gln			
305	310	315	320
Gln Arg Val Ile Thr Gln Ala Leu Ala Ser Ala Gly Leu Ser Val Ser			
325	330	335	
Asp Val Asp Ala Val Glu Ala His Gly Thr Gly Thr Arg Leu Gly Asp			
340	345	350	
Pro Ile Glu Ala Gln Ala Leu Ile Ala Thr Tyr Gly Arg Asp Arg Asp			
355	360	365	
Pro Gly Arg Pro Leu Trp Leu Gly Ser Val Lys Ser Asn Ile Gly His			
370	375	380	
Thr Gln Ala Ala Ala Gly Val Ala Gly Val Ile Lys Met Val Met Ala			
385	390	395	400
Met Arg His Gly Gln Leu Pro Arg Thr Leu His Val Glu Ser Pro Ser			
405	410	415	
Pro Glu Val Asp Trp Ser Ala Gly Thr Val Gln Leu Leu Thr Glu Asn			
420	425	430	
Thr Pro Trp Pro Arg Ser Gly Arg Val Arg Arg Val Gly Val Ser Ser			
435	440	445	
Phe Gly Ile Ser Gly Thr Asn Ala His Val Ile Leu Glu Gln Pro Pro			
450	455	460	
Gly Val Pro Ser Gln Ser Ala Gly Pro Gly Ser Gly Ser Val Val Asp			
465	470	475	480
Val Pro Val Val Pro Trp Met Val Ser Gly Lys Thr Pro Glu Ala Leu			

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485										490					495				
Ser	Ala	Gln	Ala	Thr	Ala	Leu	Met	Thr	Tyr	Leu	Asp	Glu	Arg	Pro	Asp				
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Val	Ser	Ser	Leu	Asp	Val	Gly	Tyr	Ser	Leu	Ala	Leu	Thr	Arg	Ser	Ala				
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Leu	Asp	Glu	Arg	Ala	Val	Val	Leu	Gly	Ser	Asp	Arg	Glu	Thr	Leu	Leu				
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Cys	Gly	Val	Lys	Ala	Leu	Ser	Ala	Gly	His	Glu	Ala	Ser	Gly	Leu	Val				
545					550					555					560				
Thr	Gly	Ser	Val	Gly	Ala	Gly	Gly	Arg	Ile	Gly	Phe	Val	Phe	Ser	Gly				
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Gln	Gly	Gly	Gln	Trp	Leu	Gly	Met	Gly	Arg	Gly	Leu	Tyr	Arg	Ala	Phe				
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Pro	Val	Phe	Ala	Ala	Ala	Phe	Asp	Glu	Ala	Cys	Ala	Glu	Leu	Asp	Ala				
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His	Leu	Gly	Gln	Glu	Ile	Gly	Val	Arg	Glu	Val	Val	Ser	Gly	Ser	Asp				
	610					615						620							
Ala	Gln	Leu	Leu	Asp	Arg	Thr	Leu	Trp	Ala	Gln	Ser	Gly	Leu	Phe	Ala				
625					630					635				640					
Leu	Gln	Val	Gly	Leu	Leu	Lys	Leu	Leu	Asp	Ser	Trp	Gly	Val	Arg	Pro				
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Ser	Val	Val	Leu	Gly	His	Ser	Val	Gly	Glu	Leu	Ala	Ala	Ala	Phe	Ala				
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Ala	Gly	Val	Val	Ser	Leu	Ser	Gly	Ala	Ala	Arg	Leu	Val	Ala	Gly	Arg				
		675					680						685						
Ala	Arg	Leu	Met	Gln	Ala	Leu	Pro	Ser	Gly	Gly	Gly	Met	Leu	Ala	Val				
	690					695						700							
Pro	Ala	Gly	Glu	Glu	Leu	Leu	Trp	Ser	Leu	Leu	Ala	Asp	Gln	Gly	Asp				
705					710						715				720				
Arg	Val	Gly	Ile	Ala	Ala	Val	Asn	Ala	Ala	Gly	Ser	Val	Val	Leu	Ser				
			725						730						735				
Gly	Asp	Arg	Asp	Val	Leu	Asp	Asp	Leu	Ala	Gly	Arg	Leu	Asp	Gly	Gln				

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740	745	750
Gly Ile Arg Ser Arg Trp Leu Arg Val Ser His Ala Phe His Ser Tyr		
755	760	765
Arg Met Asp Pro Met Leu Ala Glu Phe Ala Glu Leu Ala Arg Thr Val		
770	775	780
Asp Tyr Arg Arg Cys Glu Val Pro Ile Val Ser Thr Leu Thr Gly Asp		
785	790	795 800
Leu Asp Asp Ala Gly Arg Met Ser Gly Pro Asp Tyr Trp Val Arg Gln		
805	810	815
Val Arg Glu Pro Val Arg Phe Ala Asp Gly Val Gln Ala Leu Val Glu		
820	825	830
His Asp Val Ala Thr Val Val Glu Leu Gly Pro Asp Gly Ala Leu Ser		
835	840	845
Ala Leu Ile Gln Glu Cys Val Ala Ala Ser Asp His Ala Gly Arg Leu		
850	855	860
Ser Ala Val Pro Ala Met Arg Arg Asn Gln Asp Glu Ala Gln Lys Val		
865	870	875 880
Met Thr Ala Leu Ala His Val His Val Arg Gly Gly Ala Val Asp Trp		
885	890	895
Arg Ser Phe Phe Ala Gly Thr Gly Ala Lys Gln Ile Glu Leu Pro Thr		
900	905	910
Tyr Ala Phe Gln Arg Gln Arg Tyr Trp Leu Val Pro Ser Asp Ser Gly		
915	920	925
Asp Val Thr Gly Ala Gly Leu Ala Gly Ala Glu His Pro Leu Leu Gly		
930	935	940
Ala Val Val Pro Val Ala Gly Gly Asp Glu Val Leu Leu Thr Gly Arg		
945	950	955 960
Ile Ser Val Arg Thr His Pro Trp Leu Ala Glu His Arg Val Leu Gly		
965	970	975
Glu Val Ile Val Ala Gly Thr Ala Leu Leu Glu Ile Ala Leu His Ala		
980	985	990
Gly Glu Arg Leu Gly Cys Glu Arg Val Glu Glu Leu Thr Leu Glu Ala		

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995	1000	1005
Pro Leu Val Leu Pro Glu Arg Gly Ala Ile Gln Val Gln Leu Arg Val		
1010	1015	1020
Gly Ala Pro Glu Asn Ser Gly Arg Arg Pro Met Ala Leu Tyr Ser Arg		
025	1030	1035 1040
Pro Glu Gly Ala Ala Glu His Asp Trp Thr Arg His Ala Thr Gly Arg		
1045	1050	1055
Leu Ala Pro Gly Arg Gly Glu Ala Ala Gly Asp Leu Ala Asp Trp Pro		
1060	1065	1070
Ala Pro Gly Ala Leu Pro Val Asp Leu Asp Glu Phe Tyr Arg Asp Leu		
1075	1080	1085
Ala Glu Leu Gly Leu Glu Tyr Gly Pro Ile Phe Gln Gly Leu Lys Ala		
1090	1095	1100
Ala Trp Arg Gln Gly Asp Glu Val Tyr Ala Glu Ala Ala Leu Pro Gly		
1105	1110	1115 1120
Thr Glu Asp Ser Gly Phe Gly Val His Pro Ala Leu Leu Asp Ala Ala		
1125	1130	1135
Leu His Ala Thr Ala Val Arg Asp Met Asp Asp Ala Arg Leu Pro Phe		
1140	1145	1150
Gln Trp Glu Gly Val Ser Leu His Ala Lys Ala Ala Pro Ala Leu Arg		
1155	1160	1165
Val Arg Val Val Pro Ala Gly Asp Asp Ala Lys Ser Leu Leu Val Cys		
1170	1175	1180
Asp Gly Thr Gly Arg Pro Val Ile Ser Val Asp Arg Leu Val Leu Arg		
1185	1190	1195 1200
Ser Ala Ala Ala Arg Arg Thr Gly Ala Arg Arg Gln Ala His Gln Ala		
1205	1210	1215
Arg Leu Tyr Arg Leu Ser Trp Pro Thr Val Gln Leu Pro Thr Ser Ala		
1220	1225	1230
Gln Pro Pro Ser Cys Val Leu Leu Gly Thr Ser Glu Val Ser Ala Asp		
1235	1240	1245
Ile Gln Val Tyr Pro Asp Leu Arg Ser Leu Thr Ala Ala Leu Asp Ala		

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1250	1255	1260
Gly Ala Glu Pro Pro Gly Val Val Ile Ala Pro Thr Pro Pro Gly Gly		
265	1270	1275 1280
Gly Arg Thr Ala Asp Val Arg Glu Thr Thr Arg His Ala Leu Asp Leu		
1285	1290	1295
Val Gln Gly Trp Leu Ser Asp Gln Arg Leu Asn Glu Ser Arg Leu Leu		
1300	1305	1310
Leu Val Thr Gln Gly Ala Val Ala Val Glu Pro Gly Glu Pro Val Thr		
1315	1320	1325
Asp Leu Ala Gln Ala Ala Leu Trp Gly Leu Leu Arg Ser Thr Gln Thr		
1330	1335	1340
Glu His Pro Asp Arg Phe Val Leu Val Asp Val Pro Glu Pro Ala Gln		
345	1350	1355 1360
Leu Leu Pro Ala Leu Pro Gly Val Leu Ala Cys Gly Glu Pro Gln Leu		
1365	1370	1375
Ala Leu Arg Arg Gly Gly Ala His Ala Pro Arg Leu Ala Gly Leu Gly		
1380	1385	1390
Ser Asp Asp Val Leu Pro Val Pro Asp Gly Thr Gly Trp Arg Leu Glu		
1395	1400	1405
Ala Thr Arg Pro Gly Ser Leu Asp Gly Leu Ala Leu Val Asp Glu Pro		
1410	1415	1420
Thr Ala Thr Ala Pro Leu Gly Asp Gly Glu Val Arg Ile Ala Met Arg		
425	1430	1435 1440
Ala Ala Gly Val Asn Phe Arg Asp Ala Leu Ile Ala Leu Gly Met Tyr		
1445	1450	1455
Pro Gly Val Ala Ser Leu Gly Ser Glu Gly Ala Gly Val Val Val Glu		
1460	1465	1470
Thr Gly Pro Gly Val Thr Gly Leu Ala Pro Gly Asp Arg Val Met Gly		
1475	1480	1485
Met Ile Pro Lys Ala Phe Gly Pro Leu Ala Val Ala Asp His Arg Met		
1490	1495	1500
Val Thr Arg Ile Pro Ala Gly Trp Ser Phe Ala Arg Ala Ala Ser Val		

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505	1510	1515	1520
Pro Ile Val Phe Leu Thr Ala Tyr Tyr Ala Leu Val Asp Leu Ala Gly	1525	1530	1535
Leu Arg Pro Gly Glu Ser Leu Leu Val His Ser Ala Ala Gly Gly Val	1540	1545	1550
Gly Met Ala Ala Ile Gln Leu Ala Arg His Leu Gly Ala Glu Val Tyr	1555	1560	1565
Ala Thr Ala Ser Glu Asp Lys Trp Gln Ala Val Glu Leu Ser Arg Glu	1570	1575	1580
His Leu Ala Ser Ser Arg Thr Cys Asp Phe Glu Gln Gln Phe Leu Gly	585	1590	1595
Ala Thr Gly Gly Arg Gly Val Asp Val Val Leu Asn Ser Leu Ala Gly	1605	1610	1615
Glu Phe Ala Asp Ala Ser Leu Arg Met Leu Pro Arg Gly Gly Arg Phe	1620	1625	1630
Leu Glu Leu Gly Lys Thr Asp Val Arg Asp Pro Val Glu Val Ala Asp	1635	1640	1645
Ala His Pro Gly Val Ser Tyr Gln Ala Phe Asp Thr Val Glu Ala Gly	1650	1655	1660
Pro Gln Arg Ile Gly Glu Met Leu His Glu Leu Val Glu Leu Phe Glu	665	1670	1675
Gly Arg Val Leu Glu Pro Leu Pro Val Thr Ala Trp Asp Val Arg Gln	1685	1690	1695
Ala Pro Glu Ala Leu Arg His Leu Ser Gln Ala Arg His Val Gly Lys	1700	1705	1710
Leu Val Leu Thr Met Pro Pro Val Trp Asp Ala Ala Gly Thr Val Leu	1715	1720	1725
Val Thr Gly Gly Thr Gly Ala Leu Gly Ala Glu Val Ala Arg His Leu	1730	1735	1740
Val Ile Glu Arg Gly Val Arg Asn Leu Val Leu Val Ser Arg Arg Gly	745	1750	1755
Pro Ala Ala Ser Gly Ala Ala Glu Leu Val Ala Gln Leu Thr Ala Tyr			1760

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1765	1770	1775
Gly Ala Glu Val Ser Leu Gln Ala Cys Asp Val Ala Asp Arg Glu Thr 1780	1785	1790
Leu Ala Lys Val Leu Ala Ser Ile Pro Asp Glu His Pro Leu Thr Ala 1795	1800	1805
Val Val His Ala Ala Gly Val Leu Asp Asp Gly Val Ser Glu Ser Leu 1810	1815	1820
Thr Val Glu Arg Leu Asp Gln Val Leu Arg Pro Lys Val Asp Gly Ala 825	1830	1835 1840
Arg Asn Leu Leu Glu Leu Ile Asp Pro Asp Val Ala Leu Val Leu Phe 1845	1850	1855
Ser Ser Val Ser Gly Val Leu Gly Ser Gly Gly Gln Gly Asn Tyr Ala 1860	1865	1870
Ala Ala Asn Ser Phe Leu Asp Ala Leu Ala Gln Gln Arg Gln Ser Arg 1875	1880	1885
Gly Leu Pro Thr Arg Ser Leu Ala Trp Gly Pro Trp Ala Glu His Gly 1890	1895	1900
Met Ala Ser Thr Leu Arg Glu Ala Glu Gln Asp Arg Leu Ala Arg Ser 905	1910	1915 1920
Gly Leu Leu Pro Ile Ser Thr Glu Glu Gly Leu Ser Gln Phe Asp Ala 1925	1930	1935
Ala Cys Gly Gly Ala His Thr Val Val Ala Pro Val Arg Phe Ser Arg 1940	1945	1950
Leu Ser Asp Gly Asn Ala Ile Lys Phe Ser Val Leu Gln Gly Leu Val 1955	1960	1965
Gly Pro His Arg Val Asn Lys Ala Ala Thr Ala Asp Asp Ala Glu Ser 1970	1975	1980
Leu Arg Lys Arg Leu Gly Arg Leu Pro Asp Ala Glu Gln His Arg Ile 985	1990	1995 2000
Leu Leu Asp Leu Val Arg Met His Val Ala Ala Val Leu Gly Phe Ala 2005	2010	2015
Gly Ser Gln Glu Ile Thr Ala Asp Gly Thr Phe Lys Val Leu Gly Phe		

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2020	2025	2030
Asp Ser Leu Thr Val Val Glu Leu Arg Asn Arg Ile Asn Gly Ala Thr		
2035	2040	2045
Gly Leu Arg Leu Pro Ala Thr Leu Val Phe Asn Tyr Pro Thr Pro Asp		
2050	2055	2060
Ala Leu Ala Ala His Leu Val Thr Ala Leu Ser Ala Asp Arg Leu Ala		
065	2070	2075 2080
Gly Thr Phe Glu Glu Leu Asp Arg Trp Ala Ala Asn Leu Pro Thr Leu		
2085	2090	2095
Ala Arg Asp Glu Ala Thr Arg Ala Gln Ile Thr Thr Arg Leu Gln Ala		
2100	2105	2110
Ile Leu Gln Ser Leu Ala Asp Val Ser Gly Gly Thr Gly Gly Gly Ser		
2115	2120	2125
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Leu Asp Asn Asp Leu Glu Leu Pro		
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1 5 10 15		
gat ctg cac cag gcg cgc gag cgg ctg cac gag gcg gag tcg gga gag		96
Asp Leu His Gln Ala Arg Glu Arg Leu His Glu Ala Glu Ser Gly Glu		
20 25 30		
cgg gaa ccc atc gcg atc gtg gcg atg ggc tgc cgg tac ccg ggt ggg		144

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Arg	Glu	Pro	Ile	Ala	Ile	Val	Ala	Met	Gly	Cys	Arg	Tyr	Pro	Gly	Gly		
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gtg	cag	gac	ccg	gaa	ggg	ctg	tgg	aaa	ctg	gtc	gcc	tcc	ggg	ggc	gac	192	
Val	Gln	Asp	Pro	Glu	Gly	Leu	Trp	Lys	Leu	Val	Ala	Ser	Gly	Gly	Asp		
	50					55				60							
gcc	atc	ggg	gaa	ttc	ccc	gct	gat	cgt	ggg	tgg	cac	ctc	gac	gag	ctc	240	
Ala	Ile	Gly	Glu	Phe	Pro	Ala	Asp	Arg	Gly	Trp	His	Leu	Asp	Glu	Leu		
65					70				75					80			
tac	gat	ccc	gac	ccg	gat	cag	ccc	gga	acc	tgc	tac	acc	cgg	cac	ggc	288	
Tyr	Asp	Pro	Asp	Pro	Asp	Gln	Pro	Gly	Thr	Cys	Tyr	Thr	Arg	His	Gly		
				85				90						95			
ggc	ttc	ctc	cac	gac	gcc	ggc	gag	ttc	gac	gcg	gga	ttc	ttc	gac	atc	336	
Gly	Phe	Leu	His	Asp	Ala	Gly	Glu	Phe	Asp	Ala	Gly	Phe	Phe	Asp	Ile		
			100					105					110				
agc	ccc	cgt	gag	gcg	ctc	gcg	atg	gac	ccg	cag	cag	cgg	ctg	ctg	ctg	384	
Ser	Pro	Arg	Glu	Ala	Leu	Ala	Met	Asp	Pro	Gln	Gln	Arg	Leu	Leu	Leu		
		115					120					125					
gaa	atc	tcc	tgg	gag	acc	gtc	gaa	tcc	gct	ggg	atg	gac	ccg	agg	tcc	432	
Glu	Ile	Ser	Trp	Glu	Thr	Val	Glu	Ser	Ala	Gly	Met	Asp	Pro	Arg	Ser		
	130					135					140						
ttg	cgg	ggg	agc	cgc	acc	ggg	gtg	ttc	gcg	gga	ttg	atg	tac	gag	ggc	480	
Leu	Arg	Gly	Ser	Arg	Thr	Gly	Val	Phe	Ala	Gly	Leu	Met	Tyr	Glu	Gly		
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tat	gac	acc	ggc	gcc	cac	cgg	gca	gga	gaa	ggg	gtc	gaa	ggc	tat	ctc	528	
Tyr	Asp	Thr	Gly	Ala	His	Arg	Ala	Gly	Glu	Gly	Val	Glu	Gly	Tyr	Leu		
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gga	acc	ggc	aat	gcg	gga	agc	gtc	gcc	tct	ggg	cgg	gtt	gcg	tat	gcg	576	
Gly	Thr	Gly	Asn	Ala	Gly	Ser	Val	Ala	Ser	Gly	Arg	Val	Ala	Tyr	Ala		
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ttc	ggg	ttc	gag	ggc	cca	gcg	gtg	acg	gta	gac	acg	gcg	tgc	tcg	tcg	624	
Phe	Gly	Phe	Glu	Gly	Pro	Ala	Val	Thr	Val	Asp	Thr	Ala	Cys	Ser	Ser		
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tcg	ttg	gtg	gcg	ctg	cat	ttg	gcg	tgt	cag	tcg	ttg	cgg	cag	ggc	gag	672	
Ser	Leu	Val	Ala	Leu	His	Leu	Ala	Cys	Gln	Ser	Leu	Arg	Gln	Gly	Glu		
	210					215					220						
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Cys	Asp	Leu	Ala	Leu	Ala	Gly	Gly	Val	Thr	Val	Met	Ser	Thr	Pro	Glu	
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Arg	Phe	Val	Glu	Phe	Ser	Arg	Gln	Arg	Gly	Leu	Ala	Pro	Asp	Gly	Arg	
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tgt	aag	tcg	ttc	gcg	gcg	gct	gcg	gat	gga	acc	ggg	tgg	ggg	gag	ggg	816
Cys	Lys	Ser	Phe	Ala	Ala	Ala	Ala	Asp	Gly	Thr	Gly	Trp	Gly	Glu	Gly	
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gcc	ggg	ttg	gtg	ttg	ctg	gag	cgg	ctg	tca	gac	gcc	agg	cgg	aac	ggg	864
Ala	Gly	Leu	Val	Leu	Leu	Glu	Arg	Leu	Ser	Asp	Ala	Arg	Arg	Asn	Gly	
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cat	cgg	gta	ctg	gcg	gtt	gtt	cgt	ggg	agc	gcg	gtg	aat	cag	gac	ggg	912
His	Arg	Val	Leu	Ala	Val	Val	Arg	Gly	Ser	Ala	Val	Asn	Gln	Asp	Gly	
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gcg	tcg	aac	gga	ttg	acg	gcc	ccg	aac	ggg	ctg	gcc	cag	gag	cgg	gtc	960
Ala	Ser	Asn	Gly	Leu	Thr	Ala	Pro	Asn	Gly	Leu	Ala	Gln	Glu	Arg	Val	
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att	cag	cag	gtg	ctc	acg	agt	gcg	ggg	ctg	tcg	gcg	tcc	gat	gtg	gac	1008
Ile	Gln	Gln	Val	Leu	Thr	Ser	Ala	Gly	Leu	Ser	Ala	Ser	Asp	Val	Asp	
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gct	gtg	gag	gcg	cat	gga	acg	ggg	acg	cgg	ctt	ggg	gat	ccg	atc	gag	1056
Ala	Val	Glu	Ala	His	Gly	Thr	Gly	Thr	Arg	Leu	Gly	Asp	Pro	Ile	Glu	
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gcg	cag	gct	ctg	ata	gcc	gcc	tat	gga	cag	gat	cgg	gac	cgg	gac	cgg	1104
Ala	Gln	Ala	Leu	Ile	Ala	Ala	Tyr	Gly	Gln	Asp	Arg	Asp	Arg	Asp	Arg	
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ccg	ctg	tgg	ttg	ggg	tcg	gtc	aag	tcc	aac	atc	ggg	cat	acg	cag	gcg	1152
Pro	Leu	Trp	Leu	Gly	Ser	Val	Lys	Ser	Asn	Ile	Gly	His	Thr	Gln	Ala	
			370				375				380					
gct	gcg	ggc	gtc	gct	ggg	gtg	atc	aag	atg	gtc	atg	gcg	atg	cgg	cac	1200
Ala	Ala	Gly	Val	Ala	Gly	Val	Ile	Lys	Met	Val	Met	Ala	Met	Arg	His	
385					390					395				400		
ggg	gag	ctg	ccg	cgc	acg	ttg	cac	gtg	gac	gag	ccg	aat	tcg	cac	gtg	1248
Gly	Glu	Leu	Pro	Arg	Thr	Leu	His	Val	Asp	Glu	Pro	Asn	Ser	His	Val	
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gac	tgg	tcg	gct	ggg	gcg	gtc	cga	ctc	ctg	acc	gag	aac	atc	cgc	tgg	1296

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Asp	Trp	Ser	Ala	Gly	Ala	Val	Arg	Leu	Leu	Thr	Glu	Asn	Ile	Arg	Trp		
			420					425					430				
cca	ggg	acg	ggg	acg	cgc	cgc	gct	gga	gtg	tcg	tcg	ttc	ggg	gta	agc	1344	
Pro	Gly	Thr	Gly	Thr	Arg	Arg	Ala	Gly	Val	Ser	Ser	Phe	Gly	Val	Ser		
		435					440					445					
ggg	acc	aac	gca	cac	gtc	atc	ctc	gaa	cac	gac	ccg	ctc	gcc	gtg	acc	1392	
Gly	Thr	Asn	Ala	His	Val	Ile	Leu	Glu	His	Asp	Pro	Leu	Ala	Val	Thr		
	450					455				460							
gag	aac	gag	gaa	gca	gcg	cag	tcc	cca	gca	cct	ggg	atc	gtg	ccc	tgg	1440	
Glu	Asn	Glu	Glu	Ala	Ala	Gln	Ser	Pro	Ala	Pro	Gly	Ile	Val	Pro	Trp		
465				470					475				480				
gcg	ttg	tcc	ggg	cgg	tcg	tcg	acg	gcg	ctg	cgg	gcc	cag	gcc	gaa	cgg	1488	
Ala	Leu	Ser	Gly	Arg	Ser	Ser	Thr	Ala	Leu	Arg	Ala	Gln	Ala	Glu	Arg		
			485					490				495					
ctg	cgc	gag	ctg	tgc	gag	cag	acc	gat	ccc	gac	ccc	gtc	gat	gtc	ggg	1536	
Leu	Arg	Glu	Leu	Cys	Glu	Gln	Thr	Asp	Pro	Asp	Pro	Val	Asp	Val	Gly		
		500						505				510					
ttc	tca	ctg	gcc	gcc	acg	cgc	acg	gct	tgg	gag	cac	cga	gcg	gtg	gtg	1584	
Phe	Ser	Leu	Ala	Ala	Thr	Arg	Thr	Ala	Trp	Glu	His	Arg	Ala	Val	Val		
	515						520					525					
ctt	ggg	cgg	gac	agc	gct	acg	ttg	cgc	tcc	ggg	ctt	ggc	gtt	gtt	gcc	1632	
Leu	Gly	Arg	Asp	Ser	Ala	Thr	Leu	Arg	Ser	Gly	Leu	Gly	Val	Val	Ala		
	530					535				540							
agc	ggg	gaa	cca	gcg	gtc	gat	gtc	gtt	gag	ggg	agc	gtc	ctg	gac	ggc	1680	
Ser	Gly	Glu	Pro	Ala	Val	Asp	Val	Val	Glu	Gly	Ser	Val	Leu	Asp	Gly		
545				550					555			560					
gag	gtc	gtc	ttc	gtc	ttc	ccc	ggg	cag	ggc	tgg	cag	tgg	gcc	ggg	atg	1728	
Glu	Val	Val	Phe	Val	Phe	Pro	Gly	Gln	Gly	Trp	Gln	Trp	Ala	Gly	Met		
			565					570				575					
gca	gtc	gac	ctg	ctg	gac	gct	tcg	ccg	acg	ttc	gcg	cgc	cac	atg	gac	1776	
Ala	Val	Asp	Leu	Leu	Asp	Ala	Ser	Pro	Thr	Phe	Ala	Arg	His	Met	Asp		
		580						585				590					
gag	tgc	gcc	acc	gcg	ctg	cgg	agg	tac	gtg	gac	tgg	tcg	ttg	gtc	gac	1824	
Glu	Cys	Ala	Thr	Ala	Leu	Arg	Arg	Tyr	Val	Asp	Trp	Ser	Leu	Val	Asp		
	595					600					605						
gtg	ctg	cgc	gga	gcg	gag	aac	tcc	cca	ccg	ctg	gac	cgg	gtg	gac	gtg	1872	

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Val	Leu	Arg	Gly	Ala	Glu	Asn	Ser	Pro	Pro	Leu	Asp	Arg	Val	Asp	Val		
610						615					620						
ctc	cag	ccc	gcg	tcc	ttc	gcg	gtg	atg	gtg	tcg	ctc	gcc	gag	gtg	tgg	1920	
Leu	Gln	Pro	Ala	Ser	Phe	Ala	Val	Met	Val	Ser	Leu	Ala	Glu	Val	Trp		
625					630					635					640		
cgt	tcc	tac	ggg	gtg	agg	ccg	gcg	gcc	gtc	gtc	ggc	cac	agt	caa	ggc	1968	
Arg	Ser	Tyr	Gly	Val	Arg	Pro	Ala	Ala	Val	Val	Gly	His	Ser	Gln	Gly		
				645					650					655			
gaa	atc	gcc	gcg	gcc	tgc	gca	gcc	ggg	gtg	ctg	ccg	ctg	gag	gat	gcg	2016	
Glu	Ile	Ala	Ala	Ala	Cys	Ala	Ala	Gly	Val	Leu	Pro	Leu	Glu	Asp	Ala		
			660					665					670				
gcc	agg	ctt	gtc	gca	ttg	cgc	agc	aga	gcg	ttg	aag	gga	ctt	tcg	ggg	2064	
Ala	Arg	Leu	Val	Ala	Leu	Arg	Ser	Arg	Ala	Leu	Lys	Gly	Leu	Ser	Gly		
		675				680						685					
cgg	ggt	ggc	atg	gcg	tcg	ctg	gcc	tgc	cct	gcg	gat	gag	gtc	gcg	gca	2112	
Arg	Gly	Gly	Met	Ala	Ser	Leu	Ala	Cys	Pro	Ala	Asp	Glu	Val	Ala	Ala		
690						695					700						
ttg	ttc	gcg	gga	tcg	ggc	ggc	cgt	ctg	gaa	gtt	gcg	gcg	atc	aac	ggc	2160	
Leu	Phe	Ala	Gly	Ser	Gly	Gly	Arg	Leu	Glu	Val	Ala	Ala	Ile	Asn	Gly		
705					710					715					720		
ccg	cga	tcg	gtc	gtg	gtg	tcc	ggc	gat	ctg	gaa	gcg	gtg	gac	gaa	ctg	2208	
Pro	Arg	Ser	Val	Val	Val	Ser	Gly	Asp	Leu	Glu	Ala	Val	Asp	Glu	Leu		
			725						730				735				
ctg	gca	gag	tgc	gct	gaa	aag	gac	atg	cgt	gca	cgc	cgt	atc	ccc	gtc	2256	
Leu	Ala	Glu	Cys	Ala	Glu	Lys	Asp	Met	Arg	Ala	Arg	Arg	Ile	Pro	Val		
			740					745					750				
gac	tac	gcc	tcg	cat	tca	gcg	cac	gtg	gag	gtg	gtt	cgg	agc	ccg	gtg	2304	
Asp	Tyr	Ala	Ser	His	Ser	Ala	His	Val	Glu	Val	Val	Arg	Ser	Pro	Val		
		755					760					765					
ctg	gcg	gcc	gcc	gcc	ggg	gtg	cga	cac	cgg	gac	ggc	cag	gtg	ccg	tgg	2352	
Leu	Ala	Ala	Ala	Ala	Gly	Val	Arg	His	Arg	Asp	Gly	Gln	Val	Pro	Trp		
770						775					780						
tgg	tcg	acg	gtg	atc	ggc	gac	tgg	gtg	gat	ccg	gcc	agg	ctg	gac	ggc	2400	
Trp	Ser	Thr	Val	Ile	Gly	Asp	Trp	Val	Asp	Pro	Ala	Arg	Leu	Asp	Gly		
785					790					795					800		
gag	tat	tgg	tat	cgg	aac	ctc	cgg	cag	ccg	gtc	cgg	ttc	gaa	cac	gcc	2448	

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Glu Tyr Trp Tyr Arg Asn Leu Arg Gln Pro Val Arg Phe Glu His Ala	
805 810 815	
gtg cag ggc ctg gtc gag cgg gga ttc ggc ctg ttc atc gaa atg agt	2496
Val Gln Gly Leu Val Glu Arg Gly Phe Gly Leu Phe Ile Glu Met Ser	
820 825 830	
gcg cat ccg gtg ctg acc acg gcg gtc gag gaa acc ggt gcg gag tcg	2544
Ala His Pro Val Leu Thr Thr Ala Val Glu Glu Thr Gly Ala Glu Ser	
835 840 845	
gag acc gcc gtg gcc gcg gta ggt acc ttg cga cgt gac tcg ggc ggc	2592
Glu Thr Ala Val Ala Ala Val Gly Thr Leu Arg Arg Asp Ser Gly Gly	
850 855 860	
ctc cgg agg ttg ttg cat tcg ctg gcc gag gcg tac gtg cgc ggc gcc	2640
Leu Arg Arg Leu Leu His Ser Leu Ala Glu Ala Tyr Val Arg Gly Ala	
865 870 875 880	
acc gtg gac tgg gcc gtg gcg ttc ggg ggc gcg ggc cga cgg ctg gac	2688
Thr Val Asp Trp Ala Val Ala Phe Gly Gly Ala Gly Arg Arg Leu Asp	
885 890 895	
ctg ccg acc tac ccg ttc cag cgc cag cgg tac tgg ctg gac aag gga	2736
Leu Pro Thr Tyr Pro Phe Gln Arg Gln Arg Tyr Trp Leu Asp Lys Gly	
900 905 910	
gct gcc tcc gac gag gct cgt gcg gtc tcg gac ccg gcg gcg ggc tgg	2784
Ala Ala Ser Asp Glu Ala Arg Ala Val Ser Asp Pro Ala Ala Gly Trp	
915 920 925	
ttc tgg caa gcc gtg gcg cgc caa gac ctg aaa agc gtg tcc gat gcc	2832
Phe Trp Gln Ala Val Ala Arg Gln Asp Leu Lys Ser Val Ser Asp Ala	
930 935 940	
ctc gat ctc gac gcc gac gca ccg ctg agc gca aca ctt cca gcc ctg	2880
Leu Asp Leu Asp Ala Asp Ala Pro Leu Ser Ala Thr Leu Pro Ala Leu	
945 950 955 960	
tcc gtc tgg cac cgt cag gaa cga gaa agg gtc ttg gca gac ggt tgg	2928
Ser Val Trp His Arg Gln Glu Arg Glu Arg Val Leu Ala Asp Gly Trp	
965 970 975	
cgg tac cga gtc gac tgg gta cgg gtg gcc ccg cag ccg gtc cgg aga	2976
Arg Tyr Arg Val Asp Trp Val Arg Val Ala Pro Gln Pro Val Arg Arg	
980 985 990	
acg cgg gaa acc tgg ctc ctg gtc gtt ccc ccg ggc ggc atc gag gaa	3024

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Thr Arg Glu Thr Trp Leu Leu Val Val Pro Pro Gly Gly Ile Glu Glu	
995	1000 1005
gcg ctg gtc gaa cgg ctg acg gat gcg ttg aac acg cga ggg atc agc	3072
Ala Leu Val Glu Arg Leu Thr Asp Ala Leu Asn Thr Arg Gly Ile Ser	
1010	1015 1020
acc ctg cgc ctc gac gtg cca ccg gcg gcg acc agt ggc gaa ctc gca	3120
Thr Leu Arg Leu Asp Val Pro Pro Ala Ala Thr Ser Gly Glu Leu Ala	
1025	1030 1035 1040
acc gaa ctc cgc gcc gca gcc gac ggt gac ccg gtg aag gca atc ctg	3168
Thr Glu Leu Arg Ala Ala Ala Asp Gly Asp Pro Val Lys Ala Ile Leu	
	1045 1050 1055
tcg ctc acc gcg ttg gac gag cga ccc cac ccc gaa tgc aag gac gtc	3216
Ser Leu Thr Ala Leu Asp Glu Arg Pro His Pro Glu Cys Lys Asp Val	
	1060 1065 1070
ccg agc ggg att gcc ttg ctg ctg aac ctg gtc aag gcg ctc ggt gaa	3264
Pro Ser Gly Ile Ala Leu Leu Leu Asn Leu Val Lys Ala Leu Gly Glu	
	1075 1080 1085
gcc gac ctc aga att cct ctg tgg acc atc acg cgt ggt gcg gtc aag	3312
Ala Asp Leu Arg Ile Pro Leu Trp Thr Ile Thr Arg Gly Ala Val Lys	
	1090 1095 1100
gca ggc ccc gca gat cgg ctg ctg cgc ccg atg cag gcg caa gca tgg	3360
Ala Gly Pro Ala Asp Arg Leu Leu Arg Pro Met Gln Ala Gln Ala Trp	
	1105 1110 1115 1120
ggt ctg ggg cga gta gcc gca ctc gaa cac ccc gag cgc tgg ggt ggg	3408
Gly Leu Gly Arg Val Ala Ala Leu Glu His Pro Glu Arg Trp Gly Gly	
	1125 1130 1135
ctg atc gac ctg ccg gat tcg ctg gac ggc gac gtc ctc acg agg ctg	3456
Leu Ile Asp Leu Pro Asp Ser Leu Asp Gly Asp Val Leu Thr Arg Leu	
	1140 1145 1150
ggc gaa gcg ctc acc aac ggc ttg gcg gaa gac caa ctg gcg att cgc	3504
Gly Glu Ala Leu Thr Asn Gly Leu Ala Glu Asp Gln Leu Ala Ile Arg	
	1155 1160 1165
cag tcg ggc gtg ctg gcc cgg cga ctg gta ccc gcc ccg gcg aat cag	3552
Gln Ser Gly Val Leu Ala Arg Arg Leu Val Pro Ala Pro Ala Asn Gln	
	1170 1175 1180
ccc gct gga cgt aag tgg cgc ccc cga ggg agc gcg ctg atc acg ggc	3600

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Gly Glu His Leu Arg Arg Arg Gly Ile Arg Pro Met Pro Ala Ala Ser	
1380	1385 1390
gcc atc ctg gct ctg cag gaa gta ctt gac cag gat gag acg tgc gtg	4224
Ala Ile Leu Ala Leu Gln Glu Val Leu Asp Gln Asp Glu Thr Cys Val	
1395	1400 1405
tcg atc gct gat gtg gac tgg gac cga ttc gtt ccc acg ttc gcc gcg	4272
Ser Ile Ala Asp Val Asp Trp Asp Arg Phe Val Pro Thr Phe Ala Ala	
1410	1415 1420
act cgc gcc acc cgg ttg ttc gac gaa gtg ccg gcg gcg aga aag gcg	4320
Thr Arg Ala Thr Arg Leu Phe Asp Glu Val Pro Ala Ala Arg Lys Ala	
1425	1430 1435 1440
atg ccc gcg aat ggg ccg gca gaa cca ggc ggc tcg ccg ttc gcc cgc	4368
Met Pro Ala Asn Gly Pro Ala Glu Pro Gly Gly Ser Pro Phe Ala Arg	
1445	1450 1455
aat ctc gcg gag ctg ccg gaa gcc caa cga cgc cac gaa ctg gtg gat	4416
Asn Leu Ala Glu Leu Pro Glu Ala Gln Arg Arg His Glu Leu Val Asp	
1460	1465 1470
ctg gtg tgc gcc cag gtg gca acc gtg ctc ggg cac ggc agt cgc gag	4464
Leu Val Cys Ala Gln Val Ala Thr Val Leu Gly His Gly Ser Arg Glu	
1475	1480 1485
gaa gtc cag ccc gag cgg gcg ttc cgc gcg ctc ggg ttc gac tcc ctc	4512
Glu Val Gln Pro Glu Arg Ala Phe Arg Ala Leu Gly Phe Asp Ser Leu	
1490	1495 1500
atg gcg gtg gat ctg cgc aat cgt ttg acc acc gcc acc ggg ttg cgc	4560
Met Ala Val Asp Leu Arg Asn Arg Leu Thr Thr Ala Thr Gly Leu Arg	
1505	1510 1515 1520
ctg ccg acc aca acc gtc ttc gac tac ccg aat ccg gcc gcc ttg gcc	4608
Leu Pro Thr Thr Thr Val Phe Asp Tyr Pro Asn Pro Ala Ala Leu Ala	
1525	1530 1535
gct cac ctg ctc gag gag ctg gtg ggt gat gtc gcg tcg gct gcg gtg	4656
Ala His Leu Leu Glu Glu Leu Val Gly Asp Val Ala Ser Ala Ala Val	
1540	1545 1550
acc gct gcc agc gcg ccc gcg agt gac gaa ccg atc gcg atc gtc gcg	4704
Thr Ala Ala Ser Ala Pro Ala Ser Asp Glu Pro Ile Ala Ile Val Ala	
1555	1560 1565
atg agc tgc cgg ttt ccg ggt ggc gcg cac tcg ccg gaa gac ctg tgg	4752

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Met Ser Cys Arg Phe Pro Gly Gly Ala His Ser Pro Glu Asp Leu Trp	
1570	1575 1580
cgg ctg gtc gcc gcc ggc acg gag gtg atc ggc gag ttc ccc tcc gac	4800
Arg Leu Val Ala Ala Gly Thr Glu Val Ile Gly Glu Phe Pro Ser Asp	
1585	1590 1595 1600
cgg ggc tgg gat gcg gaa ggc ctt tac gat ccg gat gct tcc agg cct	4848
Arg Gly Trp Asp Ala Glu Gly Leu Tyr Asp Pro Asp Ala Ser Arg Pro	
1605	1610 1615
gga acg acg tat gcg cgg atg gcg gga ttc ctc tac gac gcc ggt gag	4896
Gly Thr Thr Tyr Ala Arg Met Ala Gly Phe Leu Tyr Asp Ala Gly Glu	
1620	1625 1630
ttc gat gcc gac ctg ttc ggc atc agc cca cgt gag gcg ttg gcg atg	4944
Phe Asp Ala Asp Leu Phe Gly Ile Ser Pro Arg Glu Ala Leu Ala Met	
1635	1640 1645
gat ccg cag cag cgg ttg gtg ctc gaa atc gcc tgg gaa gcc ctc gaa	4992
Asp Pro Gln Gln Arg Leu Val Leu Glu Ile Ala Trp Glu Ala Leu Glu	
1650	1655 1660
cgg gcc gga atc gat ccg ttg tcc ttg aag ggc agt ggg gtc ggc acg	5040
Arg Ala Gly Ile Asp Pro Leu Ser Leu Lys Gly Ser Gly Val Gly Thr	
1665	1670 1675 1680
tac atc ggc gct gga agc cgt ggg tac gcg acg gat gtg cgg cag ttt	5088
Tyr Ile Gly Ala Gly Ser Arg Gly Tyr Ala Thr Asp Val Arg Gln Phe	
1685	1690 1695
ccc gag gag gcg gag ggc tac ctg ctg acg ggt acc tcg gcc agt gtg	5136
Pro Glu Glu Ala Glu Gly Tyr Leu Leu Thr Gly Thr Ser Ala Ser Val	
1700	1705 1710
ctg tcg ggt cgg gtc gcg tat tcg ttt ggt ttc gag ggt cct gcg gtg	5184
Leu Ser Gly Arg Val Ala Tyr Ser Phe Gly Phe Glu Gly Pro Ala Val	
1715	1720 1725
acg gtg gat acg gct tgt tcg tcg tcg ttg gtg gcg ttg cat ctg gcg	5232
Thr Val Asp Thr Ala Cys Ser Ser Ser Leu Val Ala Leu His Leu Ala	
1730	1735 1740
tgc cag tcg ttg cgt tcg ggc gag tgt gat ctg gcg ttg gcc ggt ggt	5280
Cys Gln Ser Leu Arg Ser Gly Glu Cys Asp Leu Ala Leu Ala Gly Gly	
1745	1750 1755 1760
gtg acc gtg atg tcg acg ccg gag atg ttc gtg gag ttc tcc cgt cag	5328

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Val Thr Val Met Ser Thr Pro Glu Met Phe Val Glu Phe Ser Arg Gln	
1765	1770 1775
cgc ggt ttg gcg ccg gat ggg cgg tgc aag tcg ttc gcg gag agc gcg	5376
Arg Gly Leu Ala Pro Asp Gly Arg Cys Lys Ser Phe Ala Glu Ser Ala	
1780	1785 1790
gac ggc acc ggc tgg ggc gaa ggc gcg ggc ctg ttg ttg ctg gag cgg	5424
Asp Gly Thr Gly Trp Gly Glu Gly Ala Gly Leu Leu Leu Leu Glu Arg	
1795	1800 1805
ttg tcg gac gcc cac cgg aat ggg cat cgg gtg ttg gcg gtg gtt cgt	5472
Leu Ser Asp Ala His Arg Asn Gly His Arg Val Leu Ala Val Val Arg	
1810	1815 1820
ggg tca gcg gtg aat cag gac ggc gcc tcg aac gga ctg gcg gcg ccg	5520
Gly Ser Ala Val Asn Gln Asp Gly Ala Ser Asn Gly Leu Ala Ala Pro	
1825	1830 1835 1840
aac ggt ccg tcg cag cag cgg gtg atc aac cag gca ctc gcg aat gcg	5568
Asn Gly Pro Ser Gln Gln Arg Val Ile Asn Gln Ala Leu Ala Asn Ala	
1845	1850 1855
gct ctt tcg gcg tcc gat gtg gat gcg gtg gag gca cat ggc acc ggg	5616
Ala Leu Ser Ala Ser Asp Val Asp Ala Val Glu Ala His Gly Thr Gly	
1860	1865 1870
acc agg ctg ggt gat ccg atc gag gcg cag gca ttg atc gca acg tat	5664
Thr Arg Leu Gly Asp Pro Ile Glu Ala Gln Ala Leu Ile Ala Thr Tyr	
1875	1880 1885
ggg cag gcc cgg gag cgg gat cgg ccc ttg tgg ctg ggg tcg gtc aag	5712
Gly Gln Ala Arg Glu Arg Asp Arg Pro Leu Trp Leu Gly Ser Val Lys	
1890	1895 1900
tcg aac atc ggt cat acg cag gcc gcg gcg ggt gtt gcc ggt gtg atc	5760
Ser Asn Ile Gly His Thr Gln Ala Ala Ala Gly Val Ala Gly Val Ile	
1905	1910 1915 1920
aag atg gtg atg gcc atg cgg cac ggg cag ctg ccc gcc tcg ctg cac	5808
Lys Met Val Met Ala Met Arg His Gly Gln Leu Pro Ala Ser Leu His	
1925	1930 1935
gcg gat gag ccc acg tcg gag gtc gat tgg tcg tcg ggg gcg gtc cgg	5856
Ala Asp Glu Pro Thr Ser Glu Val Asp Trp Ser Ser Gly Ala Val Arg	
1940	1945 1950
ctc ctc gcc gaa cag gta cct tgg ccg gag tct gac cgt gtt cgt cgg	5904

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Leu Leu Ala Glu Gln Val Pro Trp Pro Glu Ser Asp Arg Val Arg Arg	
1955	1960 1965
gtg ggg gtt tcg tcg ttc ggg atc agc ggc acc aac gca cat gtg atc	5952
Val Gly Val Ser Ser Phe Gly Ile Ser Gly Thr Asn Ala His Val Ile	
1970	1975 1980
ctc gaa caa gct acg aat gcg cca gat agt aca gcg gag acg gac aaa	6000
Leu Glu Gln Ala Thr Asn Ala Pro Asp Ser Thr Ala Glu Thr Asp Lys	
1985	1990 1995 2000
aca gaa tcc gga tct act gtc gat att ccg gtc gtt ccc tgg ttg gtg	6048
Thr Glu Ser Gly Ser Thr Val Asp Ile Pro Val Val Pro Trp Leu Val	
2005	2010 2015
tcg gga aag acg acg gat tcc ctg cgg gga caa gcc gaa cga gtc ttg	6096
Ser Gly Lys Thr Thr Asp Ser Leu Arg Gly Gln Ala Glu Arg Val Leu	
2020	2025 2030
tct cag gtc gag tcc cgg ccg gag cag cgt tcg ctg gat gtt gcc tac	6144
Ser Gln Val Glu Ser Arg Pro Glu Gln Arg Ser Leu Asp Val Ala Tyr	
2035	2040 2045
tcg ctt gct tct ggc cga gcc gcg ctg gat gaa cgc gct gtc gtg ctg	6192
Ser Leu Ala Ser Gly Arg Ala Ala Leu Asp Glu Arg Ala Val Val Leu	
2050	2055 2060
ggc gcg gac cgc ggt gag ctg gtt gct gga ctg gcg gcg ttg gcc gcc	6240
Gly Ala Asp Arg Gly Glu Leu Val Ala Gly Leu Ala Ala Leu Ala Ala	
2065	2070 2075 2080
ggc cag gag gct tct ggg gtg atc agc gga act cgt gct tct gct cgg	6288
Gly Gln Glu Ala Ser Gly Val Ile Ser Gly Thr Arg Ala Ser Ala Arg	
2085	2090 2095
ttc ggg ttc gtg ttc tcg ggg cag ggt ggt cag tgg ttg ggg atg ggc	6336
Phe Gly Phe Val Phe Ser Gly Gln Gly Gly Gln Trp Leu Gly Met Gly	
2100	2105 2110
aga gcg ctc tac tcg aag ttt ccg gtg ttc gct gct gcg ttt gat gag	6384
Arg Ala Leu Tyr Ser Lys Phe Pro Val Phe Ala Ala Ala Phe Asp Glu	
2115	2120 2125
gct tgc gcc gag ttg gag gca cat ctg ggg gaa gac cgc cgg gtt cgg	6432
Ala Cys Ala Glu Leu Glu Ala His Leu Gly Glu Asp Arg Arg Val Arg	
2130	2135 2140
gat gtg gtc ttc ggt tcc gat gcg cag ctg ctg gat cag acg ctg tgg	6480

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Asp Val Val Phe Gly Ser Asp Ala Gln Leu Leu Asp Gln Thr Leu Trp	
2145 2150 2155 2160	
gcg cag tcg ggt ctg ttc gcg ctg caa gcc ggc ctc ttg ggg ctg ctg	6528
Ala Gln Ser Gly Leu Phe Ala Leu Gln Ala Gly Leu Leu Gly Leu Leu	
2165 2170 2175	
ggt tcg tgg ggc gtt cgg ccg gat gtg gtg atg ggg cat tcg gtc ggg	6576
Gly Ser Trp Gly Val Arg Pro Asp Val Val Met Gly His Ser Val Gly	
2180 2185 2190	
gag ttg gcc gcc gcg ttt gcg gct ggc gtg ttg tcg ttg cgg gat gcg	6624
Glu Leu Ala Ala Ala Phe Ala Ala Gly Val Leu Ser Leu Arg Asp Ala	
2195 2200 2205	
gct cgg ttg gtg gcc gcg cgc gcc cgg ttg atg caa gcc ctg ccc tct	6672
Ala Arg Leu Val Ala Ala Arg Ala Arg Leu Met Gln Ala Leu Pro Ser	
2210 2215 2220	
gac ggc gcg atg ttg gcg gtg gct gct ggt gaa gac ctt gtt cgg cca	6720
Asp Gly Ala Met Leu Ala Val Ala Ala Gly Glu Asp Leu Val Arg Pro	
2225 2230 2235 2240	
ttg ctg gcc ggt cgg gag gag tcc gtg agc gtc gcc gcg ctc aat gcc	6768
Leu Leu Ala Gly Arg Glu Glu Ser Val Ser Val Ala Ala Leu Asn Ala	
2245 2250 2255	
ccc ggt tcg gtg gtg ttg tcg ggc gat cgg gag gtg ctg gcc agc atc	6816
Pro Gly Ser Val Val Leu Ser Gly Asp Arg Glu Val Leu Ala Ser Ile	
2260 2265 2270	
gtc ggc cgg ctg acc gag ctc cga gtc cgg acg cgg cgc ttg cgg gtc	6864
Val Gly Arg Leu Thr Glu Leu Arg Val Arg Thr Arg Arg Leu Arg Val	
2275 2280 2285	
tcc cat gct ttt cat tcg cac cgg atg gac ccg atg ttg ggc gag ttc	6912
Ser His Ala Phe His Ser His Arg Met Asp Pro Met Leu Gly Glu Phe	
2290 2295 2300	
gcc cag atc gcc gag tct gcg gag ttc ggt aag cca acg aca ccg ctt	6960
Ala Gln Ile Ala Glu Ser Ala Glu Phe Gly Lys Pro Thr Thr Pro Leu	
2305 2310 2315 2320	
gtg tcg acg ttg acg ggt gag ctc gac aga gcc gcg gaa atg agc aca	7008
Val Ser Thr Leu Thr Gly Glu Leu Asp Arg Ala Ala Glu Met Ser Thr	
2325 2330 2335	
cca ggg tat tgg gtg cgc cag gcg cgt gaa ccc gtc cgt ttc qcc qac	7056

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Pro Gly Tyr Trp Val Arg Gln Ala Arg Glu Pro Val Arg Phe Ala Asp	
2340	2345 2350
ggt gtc cag gcc ctg gca gcg cag ggc ata ggc acg gtc gtc gag ctc	7104
Gly Val Gln Ala Leu Ala Ala Gln Gly Ile Gly Thr Val Val Glu Leu	
2355	2360 2365
ggc ccg gac gga acg ctg gcg gca ctg gtt cgg gag tgt gcg acc gag	7152
Gly Pro Asp Gly Thr Leu Ala Ala Leu Val Arg Glu Cys Ala Thr Glu	
2370	2375 2380
tcc gat cgg gtt ggg cgg att tcg tcg atc cca ctg atg cgc agg gag	7200
Ser Asp Arg Val Gly Arg Ile Ser Ser Ile Pro Leu Met Arg Arg Glu	
2385	2390 2395 2400
cgg gac gag acc cgt tcg gtg atg aca gcc ctg gcg cat ctc cac acc	7248
Arg Asp Glu Thr Arg Ser Val Met Thr Ala Leu Ala His Leu His Thr	
2405	2410 2415
cgt ggt ggt gag gtg gac tgg cag gcg ttt ttc gcc ggt acc ggc gct	7296
Arg Gly Gly Glu Val Asp Trp Gln Ala Phe Phe Ala Gly Thr Gly Ala	
2420	2425 2430
agg cag ctc gag ttg cca acg tat gcc ttc caa cga cag cac tac tgg	7344
Arg Gln Leu Glu Leu Pro Thr Tyr Ala Phe Gln Arg Gln His Tyr Trp	
2435	2440 2445
atc gag tcc agt gcg cgg cca gca cgc gac cgc gca gac atc ggc gag	7392
Ile Glu Ser Ser Ala Arg Pro Ala Arg Asp Arg Ala Asp Ile Gly Glu	
2450	2455 2460
gtg gcg gaa cag ttc tgg acc gcg gtt gac caa ggc gat ctg gca acg	7440
Val Ala Glu Gln Phe Trp Thr Ala Val Asp Gln Gly Asp Leu Ala Thr	
2465	2470 2475 2480
ttg gtc gcc gct ctg gat ctt ggg gcg gac gac gac aca tgc gca tcg	7488
Leu Val Ala Ala Leu Asp Leu Gly Ala Asp Asp Asp Thr Cys Ala Ser	
2485	2490 2495
ttg agc gat gta ttg ccg gcg ttg tcc tcc tgg cga agc gga ctc cgc	7536
Leu Ser Asp Val Leu Pro Ala Leu Ser Ser Trp Arg Ser Gly Leu Arg	
2500	2505 2510
aac cgt tcg ctc gtc gat tcc tgc cgg tac cga atc agt tgg cat tcc	7584
Asn Arg Ser Leu Val Asp Ser Cys Arg Tyr Arg Ile Ser Trp His Ser	
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Val Pro Gly Ala Ala Asp Asp Gly Leu Val Thr Ala Leu Thr Ser Ser	
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Leu Val Gly Gly Gly Ala Glu Val Val Arg Ile Gly Leu Ser Glu Glu	
2565	2570 2575
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Asp Pro His Arg Glu Asp Val Ala Gln Arg Leu Ala Asn Ala Leu Thr	
2580	2585 2590
gat gcc ggt caa ctc ggt ggc gtg ctt tcg ctg ttg ggg ctc gat gaa	7824
Asp Ala Gly Gln Leu Gly Gly Val Leu Ser Leu Leu Gly Leu Asp Glu	
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tcg cct gct ccg gga ttc tcc tgc ttg cca act ggt ttc gcg ctg act	7872
Ser Pro Ala Pro Gly Phe Ser Cys Leu Pro Thr Gly Phe Ala Leu Thr	
2610	2615 2620
gtg cag ctt ctg cgg gcc ttg cgg aag gcc gac gtc gag gcg cct ttt	7920
Val Gln Leu Leu Arg Ala Leu Arg Lys Ala Asp Val Glu Ala Pro Phe	
2625	2630 2635 2640
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Trp Ala Val Thr Arg Gly Gly Val Ala Leu Glu Asp Val Arg Val Ser	
2645	2650 2655
ccg gag cag gcc ctg gtc tgg ggg ctg ctg cgt gtc gcg gga ctg gag	8016
Pro Glu Gln Ala Leu Val Trp Gly Leu Leu Arg Val Ala Gly Leu Glu	
2660	2665 2670
cac ccg gag ttc tgg ggt ggc ttg atc gac ctg cca tcg gac tgg gac	8064
His Pro Glu Phe Trp Gly Gly Leu Ile Asp Leu Pro Ser Asp Trp Asp	
2675	2680 2685
gac cga ttg ggt gcc cgg ttg gcg ggt gtg ttg gcg gat ggt ggc gag	8112
Asp Arg Leu Gly Ala Arg Leu Ala Gly Val Leu Ala Asp Gly Gly Glu	
2690	2695 2700
gat caa gtc gcc att cgc cgt ggt ggt gtg ttc gtg cgg cgg ttg gaa	8160
Asp Gln Val Ala Ile Arg Arg Gly Gly Val Phe Val Arg Arg Leu Glu	
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cgc gct ggt gcg tcg ggt gcc ggg tcg gtg tgg cgt cct cgg ggg acg	8208

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Val Leu Val Thr Gly Gly Thr Gly Gly Leu Gly Ala His Val Ala Arg	
2740	2745 2750
tgg ttg gcc ggt gcc ggg gct gag cac gtg gtg ttg acc agc cgt cga	8304
Trp Leu Ala Gly Ala Gly Ala Glu His Val Val Leu Thr Ser Arg Arg	
2755	2760 2765
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Gly Ala Asp Ala Pro Gly Ala Gly Glu Leu Arg Ala Glu Leu Glu Ala	
2770	2775 2780
ctg ggt gct cgg gtg tcg att gtg ccc tgc gac gtg gct gat cgt gac	8400
Leu Gly Ala Arg Val Ser Ile Val Pro Cys Asp Val Ala Asp Arg Asp	
2785	2790 2795 2800
gca gtg gct gga gtg ttg gca ggg atc ggt ggg gag tgt ccg ctg act	8448
Ala Val Ala Gly Val Leu Ala Gly Ile Gly Gly Glu Cys Pro Leu Thr	
2805	2810 2815
gcg gtg gta cac gcc gcc ggg gtc ggc gag gcg ggc gac gta gtg gag	8496
Ala Val Val His Ala Ala Gly Val Gly Glu Ala Gly Asp Val Val Glu	
2820	2825 2830
atg ggt ttg gcg gat ttt gca gcg gtg ttg tcg gcg aag gtg cgt ggt	8544
Met Gly Leu Ala Asp Phe Ala Ala Val Leu Ser Ala Lys Val Arg Gly	
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Val Met Phe Ser Ser Val Ser Gly Val Trp Gly Ala Gly Gly Gln Gly	
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Ala Tyr Ala Ala Ala Asn Ala Tyr Leu Asp Ala Leu Ala Glu Gln Arg	
2885	2890 2895
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Arg Ala Arg Gly Leu Val Gly Thr Ala Val Ala Trp Gly Pro Trp Ala	
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gca ttg gac cgc gat gag acc tcc ctc gtc gtg gcc gat gtc gat tgg 8880
 Ala Leu Asp Arg Asp Glu Thr Ser Leu Val Val Ala Asp Val Asp Trp
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 Ala Arg Phe Ala Pro Ala Phe Thr Ser Ala Arg Arg Arg Pro Leu Leu
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 Asp Thr Ile Asp Glu Ala Arg Ala Ala Leu Glu Thr Thr Gly Glu Gln
 2980 2985 2990

gcg ggc aca ggc aaa ccc gtt gag ctg acg caa cgc ctg gcc gga ctg 9024
 Ala Gly Thr Gly Lys Pro Val Glu Leu Thr Gln Arg Leu Ala Gly Leu
 2995 3000 3005

tcg cgg aag gaa cgc gac gat gcg gta ttg gat ctg gtg cgg gcg gag 9072
 Ser Arg Lys Glu Arg Asp Asp Ala Val Leu Asp Leu Val Arg Ala Glu
 3010 3015 3020

acg gcg gct gtg ctg gga cgc gac gat gcc acg gcc ctg gcg cca tcg 9120
 Thr Ala Ala Val Leu Gly Arg Asp Asp Ala Thr Ala Leu Ala Pro Ser
 3025 3030 3035 3040

cgg ccg ttc cag gaa ctc gga ttc gac tcc ttg atg gcg gtg gag ctg 9168
 Arg Pro Phe Gln Glu Leu Gly Phe Asp Ser Leu Met Ala Val Glu Leu
 3045 3050 3055

cgc aac cgg ctg aac acc gcc acc ggg atc cag ctg ccc gcc agc acg 9216
 Arg Asn Arg Leu Asn Thr Ala Thr Gly Ile Gln Leu Pro Ala Ser Thr
 3060 3065 3070

att ttc gac tac ccc aat gcc gag tcg ctg tcg cgt cac ctc tgc gcc 9264
 Ile Phe Asp Tyr Pro Asn Ala Glu Ser Leu Ser Arg His Leu Cys Ala
 3075 3080 3085

gag ctt ttc cca acg gag act acc gtg gac tcg gcc ctt gcc gag ctc 9312
 Glu Leu Phe Pro Thr Glu Thr Thr Val Asp Ser Ala Leu Ala Glu Leu
 3090 3095 3100

gat cga atc gag cag cag ctc tcg atg ctc acc ggc gaa gcg cgg gca 9360

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Asp Arg Ile Glu Gln Gln Leu Ser Met Leu Thr Gly Glu Ala Arg Ala
 3105 3110 3115 3120

 cgg gac cga atc gcg aca cga ctg cga gcc ctc cac gag aag tgg aac 9408
 Arg Asp Arg Ile Ala Thr Arg Leu Arg Ala Leu His Glu Lys Trp Asn
 3125 3130 3135

 agc gca gct gaa gta ccg acc gga gcc gat gtc ctg agc acg ctc gat 9456
 Ser Ala Ala Glu Val Pro Thr Gly Ala Asp Val Leu Ser Thr Leu Asp
 3140 3145 3150

 tcg gcg acg cac gac gag ata ttc gag ttc atc gac aac gag ctc gac 9504
 Ser Ala Thr His Asp Glu Ile Phe Glu Phe Ile Asp Asn Glu Leu Asp
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 ctg tcc tga 9513
 Leu Ser
 3170

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 <211> 3170
 <212> PRT
 <213> *Saccharopolyspora spinosa*

 <400> 46
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 1 5 10 15

 Asp Leu His Gln Ala Arg Glu Arg Leu His Glu Ala Glu Ser Gly Glu
 20 25 30

 Arg Glu Pro Ile Ala Ile Val Ala Met Gly Cys Arg Tyr Pro Gly Gly
 35 40 45

 Val Gln Asp Pro Glu Gly Leu Trp Lys Leu Val Ala Ser Gly Gly Asp
 50 55 60

 Ala Ile Gly Glu Phe Pro Ala Asp Arg Gly Trp His Leu Asp Glu Leu
 65 70 75 80

 Tyr Asp Pro Asp Pro Asp Gln Pro Gly Thr Cys Tyr Thr Arg His Gly
 85 90 95

 Gly Phe Leu His Asp Ala Gly Glu Phe Asp Ala Gly Phe Phe Asp Ile
 100 105 110

 Ser Pro Arg Glu Ala Leu Ala Met Asp Pro Gln Gln Arg Leu Leu Leu

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115		120		125
Glu Ile Ser Trp Glu Thr Val Glu Ser Ala Gly Met Asp Pro Arg Ser				
130		135		140
Leu Arg Gly Ser Arg Thr Gly Val Phe Ala Gly Leu Met Tyr Glu Gly				
145		150		155
				160
Tyr Asp Thr Gly Ala His Arg Ala Gly Glu Gly Val Glu Gly Tyr Leu				
	165		170	175
Gly Thr Gly Asn Ala Gly Ser Val Ala Ser Gly Arg Val Ala Tyr Ala				
	180		185	190
Phe Gly Phe Glu Gly Pro Ala Val Thr Val Asp Thr Ala Cys Ser Ser				
195		200		205
Ser Leu Val Ala Leu His Leu Ala Cys Gln Ser Leu Arg Gln Gly Glu				
210		215		220
Cys Asp Leu Ala Leu Ala Gly Gly Val Thr Val Met Ser Thr Pro Glu				
225		230		235
				240
Arg Phe Val Glu Phe Ser Arg Gln Arg Gly Leu Ala Pro Asp Gly Arg				
	245		250	255
Cys Lys Ser Phe Ala Ala Ala Ala Asp Gly Thr Gly Trp Gly Glu Gly				
	260		265	270
Ala Gly Leu Val Leu Leu Glu Arg Leu Ser Asp Ala Arg Arg Asn Gly				
	275		280	285
His Arg Val Leu Ala Val Val Arg Gly Ser Ala Val Asn Gln Asp Gly				
290		295		300
Ala Ser Asn Gly Leu Thr Ala Pro Asn Gly Leu Ala Gln Glu Arg Val				
305		310		315
				320
Ile Gln Gln Val Leu Thr Ser Ala Gly Leu Ser Ala Ser Asp Val Asp				
	325		330	335
Ala Val Glu Ala His Gly Thr Gly Thr Arg Leu Gly Asp Pro Ile Glu				
	340		345	350
Ala Gln Ala Leu Ile Ala Ala Tyr Gly Gln Asp Arg Asp Arg Asp Arg				
355		360		365
Pro Leu Trp Leu Gly Ser Val Lys Ser Asn Ile Gly His Thr Gln Ala				

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Ala Ala Gly Val	Ala Gly Val Ile Lys Met Val Met Ala Met Arg His			
385	390	395		400
Gly Glu Leu Pro Arg Thr Leu His Val Asp Glu Pro Asn Ser His Val				
	405	410		415
Asp Trp Ser Ala Gly Ala Val Arg Leu Leu Thr Glu Asn Ile Arg Trp				
	420	425		430
Pro Gly Thr Gly Thr Arg Arg Ala Gly Val Ser Ser Phe Gly Val Ser				
	435	440		445
Gly Thr Asn Ala His Val Ile Leu Glu His Asp Pro Leu Ala Val Thr				
	450	455		460
Glu Asn Glu Glu Ala Ala Gln Ser Pro Ala Pro Gly Ile Val Pro Trp				
465	470	475		480
Ala Leu Ser Gly Arg Ser Ser Thr Ala Leu Arg Ala Gln Ala Glu Arg				
	485	490		495
Leu Arg Glu Leu Cys Glu Gln Thr Asp Pro Asp Pro Val Asp Val Gly				
	500	505		510
Phe Ser Leu Ala Ala Thr Arg Thr Ala Trp Glu His Arg Ala Val Val				
	515	520		525
Leu Gly Arg Asp Ser Ala Thr Leu Arg Ser Gly Leu Gly Val Val Ala				
	530	535		540
Ser Gly Glu Pro Ala Val Asp Val Val Glu Gly Ser Val Leu Asp Gly				
545	550	555		560
Glu Val Val Phe Val Phe Pro Gly Gln Gly Trp Gln Trp Ala Gly Met				
	565	570		575
Ala Val Asp Leu Leu Asp Ala Ser Pro Thr Phe Ala Arg His Met Asp				
	580	585		590
Glu Cys Ala Thr Ala Leu Arg Arg Tyr Val Asp Trp Ser Leu Val Asp				
	595	600		605
Val Leu Arg Gly Ala Glu Asn Ser Pro Pro Leu Asp Arg Val Asp Val				
	610	615		620
Leu Gln Pro Ala Ser Phe Ala Val Met Val Ser Leu Ala Glu Val Trp				

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625	630	635	640
Arg Ser Tyr Gly Val	Arg Pro Ala Ala Val	Val Gly His Ser Gln Gly	
645	650	655	
Glu Ile Ala Ala Ala Cys	Ala Ala Gly Val Leu Pro	Leu Glu Asp Ala	
660	665	670	
Ala Arg Leu Val Ala Leu	Arg Ser Arg Ala Leu Lys	Gly Leu Ser Gly	
675	680	685	
Arg Gly Gly Met Ala Ser	Leu Ala Cys Pro Ala Asp	Glu Val Ala Ala	
690	695	700	
Leu Phe Ala Gly Ser Gly	Gly Arg Leu Glu Val Ala	Ala Ile Asn Gly	
705	710	715	720
Pro Arg Ser Val Val Val	Ser Gly Asp Leu Glu Ala	Val Asp Glu Leu	
725	730	735	
Leu Ala Glu Cys Ala Glu	Lys Asp Met Arg Ala Arg	Arg Ile Pro Val	
740	745	750	
Asp Tyr Ala Ser His Ser	Ala His Val Glu Val Val	Arg Ser Pro Val	
755	760	765	
Leu Ala Ala Ala Ala Gly	Val Arg His Arg Asp Gly	Gln Val Pro Trp	
770	775	780	
Trp Ser Thr Val Ile Gly	Asp Trp Val Asp Pro Ala	Arg Leu Asp Gly	
785	790	795	800
Glu Tyr Trp Tyr Arg Asn	Leu Arg Gln Pro Val Arg	Phe Glu His Ala	
805	810	815	
Val Gln Gly Leu Val Glu	Arg Gly Phe Gly Leu Phe	Ile Glu Met Ser	
820	825	830	
Ala His Pro Val Leu Thr	Thr Ala Val Glu Glu Thr	Gly Ala Glu Ser	
835	840	845	
Glu Thr Ala Val Ala Ala	Val Gly Thr Leu Arg Arg	Asp Ser Gly Gly	
850	855	860	
Leu Arg Arg Leu Leu His	Ser Leu Ala Glu Ala Tyr	Val Arg Gly Ala	
865	870	875	880
Thr Val Asp Trp Ala Val	Ala Phe Gly Gly Ala Gly	Arg Arg Leu Asp	

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885	890	895
Leu Pro Thr Tyr Pro Phe Gln Arg Gln Arg Tyr Trp Leu Asp Lys Gly		
900	905	910
Ala Ala Ser Asp Glu Ala Arg Ala Val Ser Asp Pro Ala Ala Gly Trp		
915	920	925
Phe Trp Gln Ala Val Ala Arg Gln Asp Leu Lys Ser Val Ser Asp Ala		
930	935	940
Leu Asp Leu Asp Ala Asp Ala Pro Leu Ser Ala Thr Leu Pro Ala Leu		
945	950	955
		960
Ser Val Trp His Arg Gln Glu Arg Glu Arg Val Leu Ala Asp Gly Trp		
965	970	975
Arg Tyr Arg Val Asp Trp Val Arg Val Ala Pro Gln Pro Val Arg Arg		
980	985	990
Thr Arg Glu Thr Trp Leu Leu Val Val Pro Pro Gly Gly Ile Glu Glu		
995	1000	1005
Ala Leu Val Glu Arg Leu Thr Asp Ala Leu Asn Thr Arg Gly Ile Ser		
1010	1015	1020
Thr Leu Arg Leu Asp Val Pro Pro Ala Ala Thr Ser Gly Glu Leu Ala		
1025	1030	1035
		1040
Thr Glu Leu Arg Ala Ala Ala Asp Gly Asp Pro Val Lys Ala Ile Leu		
1045	1050	1055
Ser Leu Thr Ala Leu Asp Glu Arg Pro His Pro Glu Cys Lys Asp Val		
1060	1065	1070
Pro Ser Gly Ile Ala Leu Leu Leu Asn Leu Val Lys Ala Leu Gly Glu		
1075	1080	1085
Ala Asp Leu Arg Ile Pro Leu Trp Thr Ile Thr Arg Gly Ala Val Lys		
1090	1095	1100
Ala Gly Pro Ala Asp Arg Leu Leu Arg Pro Met Gln Ala Gln Ala Trp		
1105	1110	1115
		1120
Gly Leu Gly Arg Val Ala Ala Leu Glu His Pro Glu Arg Trp Gly Gly		
1125	1130	1135
Leu Ile Asp Leu Pro Asp Ser Leu Asp Gly Asp Val Leu Thr Arg Leu		

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Gln Ser Gly Val Leu Ala Arg Arg Leu Val Pro Ala Pro Ala Asn Gln		
1170	1175	1180
Pro Ala Gly Arg Lys Trp Arg Pro Arg Gly Ser Ala Leu Ile Thr Gly		
1185	1190	1195 1200
Gly Leu Gly Ala Val Gly Ala Gln Val Ala Arg Trp Leu Ala Glu Ile		
1205	1210	1215
Gly Ala Glu Arg Ile Val Leu Thr Ser Arg Arg Gly Asn Gln Ala Ala		
1220	1225	1230
Gly Ala Ala Glu Leu Glu Ala Glu Leu Arg Ala Leu Gly Ala Gln Val		
1235	1240	1245
Ser Ile Val Ala Cys Asp Val Thr Asp Arg Ala Glu Met Ser Ala Leu		
1250	1255	1260
Leu Ala Glu Phe Asp Val Thr Ala Val Phe His Ala Ala Gly Val Gly		
1265	1270	1275 1280
Arg Leu Leu Pro Leu Ala Glu Thr Asp Gln Asn Gly Leu Ala Glu Ile		
1285	1290	1295
Cys Ala Ala Lys Val Arg Gly Ala Gln Val Leu Asp Glu Leu Cys Asp		
1300	1305	1310
Ser Thr Asp Leu Asp Ala Phe Val Leu Phe Ser Ser Gly Ala Gly Val		
1315	1320	1325
Trp Gly Gly Gly Gly Gln Gly Ala Tyr Gly Ala Ala Asn Ala Phe Leu		
1330	1335	1340
Asp Thr Leu Ala Glu Gln Arg Arg Ala Arg Gly Leu Pro Ala Thr Ser		
1345	1350	1355 1360
Ile Ser Trp Gly Ser Trp Ala Gly Gly Gly Met Ala Asp Gly Ala Ala		
1365	1370	1375
Gly Glu His Leu Arg Arg Arg Gly Ile Arg Pro Met Pro Ala Ala Ser		
1380	1385	1390
Ala Ile Leu Ala Leu Gln Glu Val Leu Asp Gln Asp Glu Thr Cys Val		

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1395	1400	1405
Ser Ile Ala Asp Val Asp Trp Asp Arg Phe Val Pro Thr Phe Ala Ala		
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Thr Arg Ala Thr Arg Leu Phe Asp Glu Val Pro Ala Ala Arg Lys Ala		
425	1430	1435 1440
Met Pro Ala Asn Gly Pro Ala Glu Pro Gly Gly Ser Pro Phe Ala Arg		
1445	1450	1455
Asn Leu Ala Glu Leu Pro Glu Ala Gln Arg Arg His Glu Leu Val Asp		
1460	1465	1470
Leu Val Cys Ala Gln Val Ala Thr Val Leu Gly His Gly Ser Arg Glu		
1475	1480	1485
Glu Val Gln Pro Glu Arg Ala Phe Arg Ala Leu Gly Phe Asp Ser Leu		
1490	1495	1500
Met Ala Val Asp Leu Arg Asn Arg Leu Thr Thr Ala Thr Gly Leu Arg		
505	1510	1515 1520
Leu Pro Thr Thr Thr Val Phe Asp Tyr Pro Asn Pro Ala Ala Leu Ala		
1525	1530	1535
Ala His Leu Leu Glu Glu Leu Val Gly Asp Val Ala Ser Ala Ala Val		
1540	1545	1550
Thr Ala Ala Ser Ala Pro Ala Ser Asp Glu Pro Ile Ala Ile Val Ala		
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Met Ser Cys Arg Phe Pro Gly Gly Ala His Ser Pro Glu Asp Leu Trp		
1570	1575	1580
Arg Leu Val Ala Ala Gly Thr Glu Val Ile Gly Glu Phe Pro Ser Asp		
585	1590	1595 1600
Arg Gly Trp Asp Ala Glu Gly Leu Tyr Asp Pro Asp Ala Ser Arg Pro		
1605	1610	1615
Gly Thr Thr Tyr Ala Arg Met Ala Gly Phe Leu Tyr Asp Ala Gly Glu		
1620	1625	1630
Phe Asp Ala Asp Leu Phe Gly Ile Ser Pro Arg Glu Ala Leu Ala Met		
1635	1640	1645
Asp Pro Gln Gln Arg Leu Val Leu Glu Ile Ala Trp Glu Ala Leu Glu		

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665	1670	1675 1680
Tyr Ile Gly Ala Gly Ser Arg Gly Tyr Ala Thr Asp Val Arg Gln Phe		
1685	1690	1695
Pro Glu Glu Ala Glu Gly Tyr Leu Leu Thr Gly Thr Ser Ala Ser Val		
1700	1705	1710
Leu Ser Gly Arg Val Ala Tyr Ser Phe Gly Phe Glu Gly Pro Ala Val		
1715	1720	1725
Thr Val Asp Thr Ala Cys Ser Ser Ser Leu Val Ala Leu His Leu Ala		
1730	1735	1740
Cys Gln Ser Leu Arg Ser Gly Glu Cys Asp Leu Ala Leu Ala Gly Gly		
745	1750	1755 1760
Val Thr Val Met Ser Thr Pro Glu Met Phe Val Glu Phe Ser Arg Gln		
1765	1770	1775
Arg Gly Leu Ala Pro Asp Gly Arg Cys Lys Ser Phe Ala Glu Ser Ala		
1780	1785	1790
Asp Gly Thr Gly Trp Gly Glu Gly Ala Gly Leu Leu Leu Leu Glu Arg		
1795	1800	1805
Leu Ser Asp Ala His Arg Asn Gly His Arg Val Leu Ala Val Val Arg		
1810	1815	1820
Gly Ser Ala Val Asn Gln Asp Gly Ala Ser Asn Gly Leu Ala Ala Pro		
825	1830	1835 1840
Asn Gly Pro Ser Gln Gln Arg Val Ile Asn Gln Ala Leu Ala Asn Ala		
1845	1850	1855
Ala Leu Ser Ala Ser Asp Val Asp Ala Val Glu Ala His Gly Thr Gly		
1860	1865	1870
Thr Arg Leu Gly Asp Pro Ile Glu Ala Gln Ala Leu Ile Ala Thr Tyr		
1875	1880	1885
Gly Gln Ala Arg Glu Arg Asp Arg Pro Leu Trp Leu Gly Ser Val Lys		
1890	1895	1900
Ser Asn Ile Gly His Thr Gln Ala Ala Ala Gly Val Ala Gly Val Ile		

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Lys Met Val Met Ala Met Arg His Gly Gln Leu Pro Ala Ser Leu His			
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1940	1945	1950	
Leu Leu Ala Glu Gln Val Pro Trp Pro Glu Ser Asp Arg Val Arg Arg			
1955	1960	1965	
Val Gly Val Ser Ser Phe Gly Ile Ser Gly Thr Asn Ala His Val Ile			
1970	1975	1980	
Leu Glu Gln Ala Thr Asn Ala Pro Asp Ser Thr Ala Glu Thr Asp Lys			
985	1990	1995	2000
Thr Glu Ser Gly Ser Thr Val Asp Ile Pro Val Val Pro Trp Leu Val			
2005	2010	2015	
Ser Gly Lys Thr Thr Asp Ser Leu Arg Gly Gln Ala Glu Arg Val Leu			
2020	2025	2030	
Ser Gln Val Glu Ser Arg Pro Glu Gln Arg Ser Leu Asp Val Ala Tyr			
2035	2040	2045	
Ser Leu Ala Ser Gly Arg Ala Ala Leu Asp Glu Arg Ala Val Val Leu			
2050	2055	2060	
Gly Ala Asp Arg Gly Glu Leu Val Ala Gly Leu Ala Ala Leu Ala Ala			
065	2070	2075	2080
Gly Gln Glu Ala Ser Gly Val Ile Ser Gly Thr Arg Ala Ser Ala Arg			
2085	2090	2095	
Phe Gly Phe Val Phe Ser Gly Gln Gly Gly Gln Trp Leu Gly Met Gly			
2100	2105	2110	
Arg Ala Leu Tyr Ser Lys Phe Pro Val Phe Ala Ala Ala Phe Asp Glu			
2115	2120	2125	
Ala Cys Ala Glu Leu Glu Ala His Leu Gly Glu Asp Arg Arg Val Arg			
2130	2135	2140	
Asp Val Val Phe Gly Ser Asp Ala Gln Leu Leu Asp Gln Thr Leu Trp			
145	2150	2155	2160
Ala Gln Ser Gly Leu Phe Ala Leu Gln Ala Gly Leu Leu Gly Leu Leu			

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Glu Leu Ala Ala Ala Phe Ala Ala Gly Val Leu Ser Leu Arg Asp Ala		
2195	2200	2205
Ala Arg Leu Val Ala Ala Arg Ala Arg Leu Met Gln Ala Leu Pro Ser		
2210	2215	2220
Asp Gly Ala Met Leu Ala Val Ala Ala Gly Glu Asp Leu Val Arg Pro		
2225	2230	2235 2240
Leu Leu Ala Gly Arg Glu Glu Ser Val Ser Val Ala Ala Leu Asn Ala		
2245	2250	2255
Pro Gly Ser Val Val Leu Ser Gly Asp Arg Glu Val Leu Ala Ser Ile		
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gtg ggc acg gtg ttt gcc ccg aag gtg acg ggg gca tgg cat ctg cac	4608
Val Gly Thr Val Phe Ala Pro Lys Val Thr Gly Ala Trp His Leu His	
1525 1530 1535	
gag ttg acc cgc gat ctg gat ctg tcg ttc ttc gtt ctt ttc tct tcc	4656
Glu Leu Thr Arg Asp Leu Asp Leu Ser Phe Phe Val Leu Phe Ser Ser	
1540 1545 1550	
ttc tcc ggg att gcg ggt gcc gca ggg cag gcc aac tac gcg gcg gcg	4704
Phe Ser Gly Ile Ala Gly Ala Ala Gly Gln Ala Asn Tyr Ala Ala Ala	
1555 1560 1565	
aac acg ttc ctg gat gca ttg gcg cgt tat cgc cgg gcg cgt ggg ctg	4752
Asn Thr Phe Leu Asp Ala Leu Ala Arg Tyr Arg Arg Ala Arg Gly Leu	
1570 1575 1580	
cct ggg ttg tcg ttg gcg tgg gga ctg tgg gcg caa ccc agc ggt atg	4800
Pro Gly Leu Ser Leu Ala Trp Gly Leu Trp Ala Gln Pro Ser Gly Met	
1585 1590 1595 1600	
acg agt ggc ttg gac gcg gcg tcg gtg gag cgg ttg gcg cgg acg ggc	4848
Thr Ser Gly Leu Asp Ala Ala Ser Val Glu Arg Leu Ala Arg Thr Gly	
1605 1610 1615	
atc gca gaa ctt tcc acg gag gat gga ctc cgc ctg ttc gat gcc gcg	4896
Ile Ala Glu Leu Ser Thr Glu Asp Gly Leu Arg Leu Phe Asp Ala Ala	
1620 1625 1630	
ttc gcg aag gac cgg gct tgc gtc gtt gcc gct cga ttg gac agg gcg	4944
Phe Ala Lys Asp Arg Ala Cys Val Val Ala Ala Arg Leu Asp Arg Ala	
1635 1640 1645	
ctg ctg gtc ggg aac gga cga tcg cac gcg att ccg gcg ctg ttg agc	4992
Leu Leu Val Gly Asn Gly Arg Ser His Ala Ile Pro Ala Leu Leu Ser	
1650 1655 1660	
gcg ttg gtt cct gtt cgc ggc ggt gtg gcg agg aaa aca gcc aat tct	5040
Ala Leu Val Pro Val Arg Gly Gly Val Ala Arg Lys Thr Ala Asn Ser	
1665 1670 1675 1680	

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Gln Ala Ala Asp Glu Asp Ala Leu Leu Gly Leu Val Arg Glu His Val	
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tcg gcc gtg ctg ggt tat tcg ggt gcg gtc gag gtt ggg ggc gac cgt	5136
Ser Ala Val Leu Gly Tyr Ser Gly Ala Val Glu Val Gly Gly Asp Arg	
1700 1705 1710	
gct ttc cgt gat ctg ggt ttt gat tcg ttg tct ggc gtg gag ttg cgg	5184
Ala Phe Arg Asp Leu Gly Phe Asp Ser Leu Ser Gly Val Glu Leu Arg	
1715 1720 1725	
aac cgc ctt gcc ggg gtg ctg ggg gtg cgg ttg ccg gcg act gcg gtg	5232
Asn Arg Leu Ala Gly Val Leu Gly Val Arg Leu Pro Ala Thr Ala Val	
1730 1735 1740	
ttc gac tat ccg acg ccg cgg gcg ctg gcg cgt ttc ctg cat cag gaa	5280
Phe Asp Tyr Pro Thr Pro Arg Ala Leu Ala Arg Phe Leu His Gln Glu	
1745 1750 1755 1760	
ctg gca ggc gag gtc gcg tcc acg tcg acg ccg gtg acc agg gca gcg	5328
Leu Ala Gly Glu Val Ala Ser Thr Ser Thr Pro Val Thr Arg Ala Ala	
1765 1770 1775	
agt gcc gaa gag gat ctt gtt gcg att gtc ggg atg gga tgt cgt ttt	5376
Ser Ala Glu Glu Asp Leu Val Ala Ile Val Gly Met Gly Cys Arg Phe	
1780 1785 1790	
ccg ggt ggg gtg tcg tcg ccg gag gag ctt tgg cgg ctg gtg gcc ggc	5424
Pro Gly Gly Val Ser Ser Pro Glu Glu Leu Trp Arg Leu Val Ala Gly	
1795 1800 1805	
ggc gtg gat gcg gtg gct ggg ttc cca gac gat cgc ggc tgg gat ctc	5472
Gly Val Asp Ala Val Ala Gly Phe Pro Asp Asp Arg Gly Trp Asp Leu	
1810 1815 1820	
gcg gcg ttg tac gat cct gat ccc gat cgt ctc ggg acc tcg tat gtg	5520
Ala Ala Leu Tyr Asp Pro Asp Pro Asp Arg Leu Gly Thr Ser Tyr Val	
1825 1830 1835 1840	
tgt gag ggc ggg ttt ctg cgg gac gcg gcg gag ttc gat gct gac atg	5568
Cys Glu Gly Gly Phe Leu Arg Asp Ala Ala Glu Phe Asp Ala Asp Met	
1845 1850 1855	
ttc ggc atc agc ccg cgt gag gcg ttg gcg atg gat ccg cag cag cgg	5616
Phe Gly Ile Ser Pro Arg Glu Ala Leu Ala Met Asp Pro Gln Gln Arg	
1860 1865 1870	

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1875 1880 1885	
ccg ttc tcg ttg cac ggc agc cgg acc ggt gtg ttc gcg ggc ttg atg	5712
Pro Phe Ser Leu His Gly Ser Arg Thr Gly Val Phe Ala Gly Leu Met	
1890 1895 1900	
tac cac gac tat ggg gcc cga ttc att acc aga gca ccg gag ggc ttc	5760
Tyr His Asp Tyr Gly Ala Arg Phe Ile Thr Arg Ala Pro Glu Gly Phe	
1905 1910 1915 1920	
gaa ggg cac ctc ggg acg ggc aat gcg ggg agc gtg ctg tcg ggt cgg	5808
Glu Gly His Leu Gly Thr Gly Asn Ala Gly Ser Val Leu Ser Gly Arg	
1925 1930 1935	
gtt gcg tat tcg ttt ggt ttc gag ggt cct gcg gtg acg gtg gat acg	5856
Val Ala Tyr Ser Phe Gly Phe Glu Gly Pro Ala Val Thr Val Asp Thr	
1940 1945 1950	
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Ala Cys Ser Ser Ser Leu Val Ala Leu His Leu Ala Gly Gln Ala Leu	
1955 1960 1965	
cgg gcc ggt gag tgc gaa ttc gcc ctt gcc ggt ggc gtc acg gtg atg	5952
Arg Ala Gly Glu Cys Glu Phe Ala Leu Ala Gly Gly Val Thr Val Met	
1970 1975 1980	
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Ser Thr Pro Thr Thr Phe Val Glu Phe Ser Arg Gln Arg Gly Leu Ala	
1985 1990 1995 2000	
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Pro Asp Gly Arg Cys Lys Ser Phe Ala Ala Ala Asp Gly Thr Gly	
2005 2010 2015	
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Trp Gly Glu Gly Ala Gly Leu Val Leu Leu Glu Arg Leu Ser Asp Ala	
2020 2025 2030	
cgg cgc aat ggg cac gag gtt ctg gcg gtg gtg cgg ggt agc gcg gtg	6144
Arg Arg Asn Gly His Glu Val Leu Ala Val Val Arg Gly Ser Ala Val	
2035 2040 2045	
aac cag gac ggc gcg tcg aat ggc ttg act gcg cca aat ggt ccg tca	6192
Asn Gln Asp Gly Ala Ser Asn Gly Leu Thr Ala Pro Asn Gly Pro Ser	
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2065					2070					2075					2080	
tcc	gac	gtg	gat	gct	gtg	gag	gcg	cat	ggg	acg	ggc	acg	cgg	ctt	ggt	6288
Ser	Asp	Val	Asp	Ala	Val	Glu	Ala	His	Gly	Thr	Gly	Thr	Arg	Leu	Gly	
				2085					2090					2095		
gat	ccg	atc	gag	gcg	cag	gcg	ttg	atc	gct	acg	tac	ggc	cgg	gat	cgt	6336
Asp	Pro	Ile	Glu	Ala	Gln	Ala	Leu	Ile	Ala	Thr	Tyr	Gly	Arg	Asp	Arg	
		2100						2105					2110			
gat	ccc	ggt	cgg	ccg	ttg	tgg	ctg	ggg	tcg	gtg	aag	tcg	aat	att	ggt	6384
Asp	Pro	Gly	Arg	Pro	Leu	Trp	Leu	Gly	Ser	Val	Lys	Ser	Asn	Ile	Gly	
		2115					2120					2125				
cac	acc	cag	gcg	gcg	gcg	ggg	gtc	gct	ggg	gtg	atc	aag	atg	gtg	atg	6432
His	Thr	Gln	Ala	Ala	Ala	Gly	Val	Ala	Gly	Val	Ile	Lys	Met	Val	Met	
	2130					2135				2140						
gcg	atg	cgg	cag	ggg	gag	ctg	ccg	cgc	acg	ttg	cac	gtg	gac	gag	ccc	6480
Ala	Met	Arg	Gln	Gly	Glu	Leu	Pro	Arg	Thr	Leu	His	Val	Asp	Glu	Pro	
2145				2150					2155					2160		
tcc	gcg	cag	gtg	gac	tgg	tct	gcg	ggc	acg	gtc	caa	ctc	ctc	acg	gag	6528
Ser	Ala	Gln	Val	Asp	Trp	Ser	Ala	Gly	Thr	Val	Gln	Leu	Leu	Thr	Glu	
			2165					2170					2175			
aac	acg	ccc	tgg	ccc	gac	agc	ggg	cgt	ctt	cgc	cgg	gcg	ggc	gtg	tca	6576
Asn	Thr	Pro	Trp	Pro	Asp	Ser	Gly	Arg	Leu	Arg	Arg	Ala	Gly	Val	Ser	
		2180					2185				2190					
tcg	ttc	ggg	atc	agt	ggc	acc	aac	gcg	cac	ctg	atc	ctt	gaa	caa	cct	6624
Ser	Phe	Gly	Ile	Ser	Gly	Thr	Asn	Ala	His	Leu	Ile	Leu	Glu	Gln	Pro	
	2195					2200				2205						
ccg	cga	gag	tcg	cag	cgc	tca	aca	gag	ccg	gat	tcg	ggg	tct	gtc	cgc	6672
Pro	Arg	Glu	Ser	Gln	Arg	Ser	Thr	Glu	Pro	Asp	Ser	Gly	Ser	Val	Arg	
	2210				2215			2220								
gat	ttt	ccg	gtg	gtg	ccg	tgg	atg	gtg	tcg	ggc	aaa	aca	ccc	gaa	gcg	6720
Asp	Phe	Pro	Val	Val	Pro	Trp	Met	Val	Ser	Gly	Lys	Thr	Pro	Glu	Ala	
2225				2230				2235					2240			
cta	tcc	gcc	cag	gca	gat	gca	ttg	atg	tcc	tac	ttg	agc	aat	cgc	gtt	6768
Leu	Ser	Ala	Gln	Ala	Asp	Ala	Leu	Met	Ser	Tyr	Leu	Ser	Asn	Arg	Val	
		2245				2250					2255					

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Ala Leu Asp His Arg Ala Val Val Leu Gly Ala Asp Arg Ala Ala Leu	
2275 2280 2285	
ctg ccg ggc ttg aaa gcg ctg gcc gtt agt aat gac gct gcc gag gtg	6912
Leu Pro Gly Leu Lys Ala Leu Ala Val Ser Asn Asp Ala Ala Glu Val	
2290 2295 2300	
atc acc ggc act cgt gcc gct ggg ccg gtc gga ttc gtg ttc tcc ggt	6960
Ile Thr Gly Thr Arg Ala Ala Gly Pro Val Gly Phe Val Phe Ser Gly	
2305 2310 2315 2320	
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Gln Gly Gly Gln Trp Pro Gly Met Gly Ser Gly Leu His Ser Ala Phe	
2325 2330 2335	
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Pro Val Phe Ala Asp Ala Phe Asp Glu Ala Cys Cys Glu Leu Asp Ala	
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His Leu Gly Gln Met Ala Arg Leu Arg Asp Val Leu Ser Gly Ser Asp	
2355 2360 2365	
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Thr Gln Leu Leu Asp Gln Thr Leu Trp Ala Gln Pro Gly Leu Phe Ala	
2370 2375 2380	
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Leu Gln Val Gly Leu Trp Glu Leu Leu Gly Ser Trp Gly Val Arg Pro	
2385 2390 2395 2400	
gct gtg gtg ctg ggc cac tcg gtc ggt gag ctg gcg gcg gcg ttc gcg	7248
Ala Val Val Leu Gly His Ser Val Gly Glu Leu Ala Ala Ala Phe Ala	
2405 2410 2415	
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Ala Gly Val Leu Ser Leu Arg Asp Ala Ala Arg Leu Val Ala Gly Arg	
2420 2425 2430	
gcc cgg ttg atg caa gcc ctg cca act ggc ggt gcc atg ctc gct gcg	7344
Ala Arg Leu Met Gln Ala Leu Pro Thr Gly Gly Ala Met Leu Ala Ala	
2435 2440 2445	

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Arg Val Gly Ile Ala Ala Val Asn Ala Pro Gly Ser Val Val Leu Ser	
2465 2470 2475 2480	
ggt gat cgg gat gtg ctc gat gac att gcc ggt cgg ctg gac ggg caa	7488
Gly Asp Arg Asp Val Leu Asp Asp Ile Ala Gly Arg Leu Asp Gly Gln	
2485 2490 2495	
ggg atc cgg tcc agg tgg ttg cgg gtt tcg cat gcg ttt cat tcg cat	7536
Gly Ile Arg Ser Arg Trp Leu Arg Val Ser His Ala Phe His Ser His	
2500 2505 2510	
cgg atg gat ccg atg ctg gcg gag ttc acc gaa atc gcc cgg agc gtg	7584
Arg Met Asp Pro Met Leu Ala Glu Phe Thr Glu Ile Ala Arg Ser Val	
2515 2520 2525	
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Asp Tyr Arg Ser Ser Gly Leu Pro Ile Val Ser Thr Leu Thr Gly Glu	
2530 2535 2540	
ctc gat gag gtc ggc atg ccg gct acg ccg gag tat tgg gtg cgc cag	7680
Leu Asp Glu Val Gly Met Pro Ala Thr Pro Glu Tyr Trp Val Arg Gln	
2545 2550 2555 2560	
gtg cga gaa ccc gtc cgc ttc gcc gac ggt gtt gct gcg ctc gcg gct	7728
Val Arg Glu Pro Val Arg Phe Ala Asp Gly Val Ala Ala Leu Ala Ala	
2565 2570 2575	
cac ggt gtg agc acc gtc gtc gag gtc ggt ccg gat ggg gtg ttg tcg	7776
His Gly Val Ser Thr Val Val Glu Val Gly Pro Asp Gly Val Leu Ser	
2580 2585 2590	
gcg ctg gtg cag gag tgc gcg gcc gga tcc gat cag ggc gga cgg gtg	7824
Ala Leu Val Gln Glu Cys Ala Ala Gly Ser Asp Gln Gly Gly Arg Val	
2595 2600 2605	
gcc gcg gtt ccg ctc atg cgc agc aat cgc gac gag gcg cac acg gtg	7872
Ala Ala Val Pro Leu Met Arg Ser Asn Arg Asp Glu Ala His Thr Val	
2610 2615 2620	
aca acg gca ttg gcg cag atc cat gtg cgt ggt gct gag gtg gac tgg	7920
Thr Thr Ala Leu Ala Gln Ile His Val Arg Gly Ala Glu Val Asp Trp	
2625 2630 2635 2640	

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Arg Ser Phe Phe Ala Gly Thr Gly Ala Lys Gln Val Glu Leu Pro Thr	
2645 2650 2655	
tat gcc ttc caa cga cag cgg tac tgg ctt gac tca cca tcc gaa ccg	8016
Tyr Ala Phe Gln Arg Gln Arg Tyr Trp Leu Asp Ser Pro Ser Glu Pro	
2660 2665 2670	
gtc ggg caa tcc gcc gat ccc gcg cgc cag tcg ggc ttc tgg gaa ctc	8064
Val Gly Gln Ser Ala Asp Pro Ala Arg Gln Ser Gly Phe Trp Glu Leu	
2675 2680 2685	
gtc gag cag gaa gat gtc agc gcg ctc agc gcc gct ctg cac att acc	8112
Val Glu Gln Glu Asp Val Ser Ala Leu Ser Ala Ala Leu His Ile Thr	
2690 2695 2700	
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Gly Asp His Asp Val Gln Ala Ser Leu Glu Ser Val Val Pro Val Leu	
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Ser Ser Trp His Arg Arg Ile Arg Asn Glu Ser Leu Val His Gln Trp	
2725 2730 2735	
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Arg Tyr Arg Ile Ser Trp His Glu Arg Ala Asp Leu Pro Asp Pro Ser	
2740 2745 2750	
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Leu Ser Gly Thr Trp Leu Val Val Val Pro Glu Gly Trp Ser Ala Ser	
2755 2760 2765	
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Arg Gln Val Leu Arg Phe Asn Glu Met Phe Glu Glu Arg Gly Cys Pro	
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Ala Val Leu Phe Glu Leu Ala Gly His Asp Glu Glu Ala Leu Ala Gln	
2785 2790 2795 2800	
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Arg Phe Arg Ser Leu Pro Val Ala Ser Gly Gly Ile Ser Gly Val Leu	
2805 2810 2815	
tcc ttg ctg gcg ctg gat gaa tcg ccg tcc tcg ccg aac gct gct ttg	8496
Ser Leu Leu Ala Leu Asp Glu Ser Pro Ser Ser Pro Asn Ala Ala Leu	
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Ala Asp Val Ser Ala Pro Leu Trp Leu Ala Thr Cys Gly Gly Val Ala	
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Val Gly Asp Val Pro Val Asn Pro Gly Gln Ala Leu Val Trp Gly Leu	
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Gly Arg Val Val Gly Leu Glu His Pro Ala Trp Trp Gly Gly Leu Val	
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Asp Val Pro Cys Leu Leu Asp Glu Asp Ala Arg Glu Arg Leu Ser Val	
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Val Leu Ala Gly Leu Gly Glu Asp Glu Ile Ala Val Arg Pro Gly Gly	
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Val Phe Val Arg Arg Leu Glu Arg Ala Gly Ala Ala Ser Gly Ala Gly	
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Ser Val Trp Arg Pro Arg Gly Thr Val Leu Val Thr Gly Gly Thr Gly	
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Gly Leu Gly Ala His Val Ala Arg Trp Leu Ala Gly Ala Gly Ala Glu	
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His Val Val Leu Thr Ser Arg Arg Gly Ala Ala Ala Pro Gly Ala Gly	
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Asp Leu Arg Ala Glu Leu Glu Ala Leu Gly Ala Arg Val Ser Ile Thr	
2995 3000 3005	
gcc tgc gac gtg gcc gat cgt gac gct ttg gcc gaa gtg ttg gcg acc	9072
Ala Cys Asp Val Ala Asp Arg Asp Ala Leu Ala Glu Val Leu Ala Thr	
3010 3015 3020	

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Ile Pro Asp Asp Cys Pro Leu Thr Ala Val Met His Ala Ala Gly Val
3025 3030 3035 3040

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Val Glu Val Gly Asp Val Ala Ser Met Cys Leu Thr Asp Phe Val Gly
3045 3050 3055

gtg ctg tcg gcg aag gca ggt ggt gcg gcg aat ctc gat gag ttg ctc 9216
Val Leu Ser Ala Lys Ala Gly Gly Ala Ala Asn Leu Asp Glu Leu Leu
3060 3065 3070

gcc gat gtc gag ctg gat gcc ttc gtg ctg ttc tca tcc gtc tcg ggt 9264
Ala Asp Val Glu Leu Asp Ala Phe Val Leu Phe Ser Ser Val Ser Gly
3075 3080 3085

gtg tgg ggt gct ggc ggg cag ggc gct tat gcg gcg gcg aat gcc tac 9312
Val Trp Gly Ala Gly Gly Gln Gly Ala Tyr Ala Ala Ala Asn Ala Tyr
3090 3095 3100

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Leu Asp Ala Leu Ala Gln Gln Arg Arg Ala Arg Gly Leu Val Gly Thr
3105 3110 3115 3120

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3125 3130 3135

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Gly Gly Ala Gln Leu Arg Arg Ala Gly Leu Val Pro Met Ala Ala Asp
3140 3145 3150

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Arg Ala Leu Leu Ala Leu Gln Gly Ala Leu Asp Arg Asp Glu Thr Ser
3155 3160 3165

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Leu Val Val Ala Asp Met Ala Trp Glu Arg Phe Ala Pro Val Phe Ala
3170 3175 3180

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Met Ser Arg Arg Arg Pro Leu Leu Asp Glu Leu Pro Glu Ala Gln Gln
3185 3190 3195 3200

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Ala Leu Ala Asp Ala Glu Asn Thr Thr Asp Ala Ala Asp Ser Ala Val
3205 3210 3215

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Met Leu Asp Leu Val Leu Ala Glu Ala Ser Ile Val Leu Gly His Asn	
3235 3240 3245	
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Gly Ser Asp Pro Val Gly Pro Asp Arg Ala Phe Gln Glu Leu Gly Phe	
3250 3255 3260	
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Thr Thr Val Val Ala Gly Ala Asp Pro Val Asp Asp Pro Val Val Val	
3315 3320 3325	
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Val Ala Met Gly Cys Arg Tyr Pro Gly Asp Val Cys Ser Pro Glu Glu	
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Gly Phe Leu Ala Gly Ala Gly Asp Phe Asp Pro Ala Met Phe Gly Ile
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 565 570 575

Gln Gly Gly Gln Trp Pro Gly Met Gly Arg Gly Leu Tyr Ser Val Phe
 580 585 590

Pro Val Phe Ala Asp Ala Phe Asp Glu Ala Cys Ala Glu Leu Asp Ala
 595 600 605

His Leu Gly Gln Glu Leu Arg Val Arg Asp Val Val Phe Gly Ser Gln
 610 615 620

Ala Trp Leu Leu Asp Arg Thr Val Trp Ala Gln Ser Gly Leu Phe Ala
 625 630 635 640

Leu Gln Ile Gly Leu Leu Arg Leu Leu Gly Ser Trp Gly Val Arg Pro
 645 650 655

Asp Val Val Leu Gly His Ser Val Gly Glu Leu Ala Ala Val His Ala
 660 665 670

Ala Gly Val Leu Ser Leu Ser Glu Ala Ala Arg Leu Val Ala Gly Arg
 675 680 685

Ala Arg Leu Met Gln Ala Leu Pro Ser Gly Gly Ala Met Leu Ala Val
 690 695 700

Ala Thr Gly Glu Phe Gln Val Asp Pro Leu Leu Asp Gly Val Arg Asp
 705 710 715 720

Arg Ile Gly Ile Ala Ala Val Asn Gly Pro Glu Ser Val Val Leu Ser
 725 730 735

Gly Asp Arg Glu Leu Leu Thr Glu Ile Ala Asp Arg Leu His Asp Gln
 740 745 750

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Gly Cys Arg Thr Arg Trp Leu Arg Val Ser His Ala Phe His Ser Pro
 755 760 765
 His Met Glu Pro Met Leu Glu Glu Phe Ala Gln Ile Ser Arg Gly Arg
 770 775 780
 Glu Tyr His Ala Pro Glu Leu Pro Ile Ile Ser Thr Leu Ile Gly Glu
 785 790 795 800
 Leu Asp Gly Gly Arg Val Met Gly Thr Pro Glu Tyr Trp Val Arg Gln
 805 810 815
 Val Arg Glu Pro Val Arg Phe Ala Glu Gly Val Gln Ala Leu Val Gly
 820 825 830
 Gln Gly Val Gly Thr Ile Val Glu Leu Gly Pro Asp Gly Ala Leu Ser
 835 840 845
 Thr Leu Val Glu Glu Cys Val Ala Glu Ser Gly Arg Val Ala Gly Ile
 850 855 860
 Pro Leu Met Arg Lys Asp Arg Asp Glu Ala Arg Thr Val Leu Ala Ala
 865 870 875 880
 Leu Ala Gln Ile His Thr Arg Gly Gly Glu Val Asp Trp Arg Ser Phe
 885 890 895
 Phe Ala Gly Thr Gly Ala Lys Gln Val Asp Leu Pro Thr Tyr Ala Phe
 900 905 910
 Gln Arg Gln Arg Tyr Trp Leu Ala Ser Thr Gly Arg Ala Gly Asp Val
 915 920 925
 Thr Ala Ala Gly Leu Ala Glu Ala Asp His Pro Leu Leu Gly Ala Val
 930 935 940
 Val Ala Leu Ala Asp Gly Glu Gly Val Val Leu Thr Gly Arg Leu Thr
 945 950 955 960
 Ala Gly Ser His Pro Trp Leu Ser Asp His Arg Val Leu Gly Glu Ile
 965 970 975
 Val Val Pro Gly Thr Ala Ile Val Glu Leu Val Trp His Val Gly Glu
 980 985 990
 Arg Leu Gly Cys Gly Arg Val Glu Glu Leu Ala Leu Glu Ala Pro Leu
 995 1000 1005

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Ile Leu Pro Asp His Gly Ala Val Gln Val Gln Val Leu Val Gly Pro
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Pro Gly Glu Ser Gly Ala Arg Ser Val Ala Leu Tyr Ser Cys Pro Gly
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Glu Ala Ile Glu Pro Glu Trp Lys Lys His Ala Thr Gly Val Leu Leu
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Pro Pro Val Ala Ala Glu Asn His Glu Leu Thr Ala Trp Pro Pro Glu
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Asn Ala Thr Glu Ile Asp Ala Asp Gly Val Tyr Ala Phe Leu Glu Gly
 1075 1080 1085

His Gly Phe Ala Tyr Gly Pro Ala Phe Arg Cys Leu Arg Gly Ala Trp
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Arg Arg Gly Gly Glu Val Phe Ala Glu Val Ala Leu Pro Asp Asp Met
 105 1110 1115 1120

Gln Ala Gly Val Asp Arg Phe Gly Val His Pro Ala Leu Leu Asp Ala
 1125 1130 1135

Val Leu His Ala Ala Ala Glu Thr Ser Val Val Gln Ser Glu Ala
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Arg Val Pro Phe Ser Trp Arg Gly Val Glu Leu Arg Ala Thr Glu Ser
 1155 1160 1165

Ala Val Val Arg Ala Arg Leu Ser Leu Thr Ser Asp Asp Glu Leu Ser
 1170 1175 1180

Leu Val Ala Val Asp Pro Ala Gly Arg Phe Val Ala Thr Val Asp Ser
 185 1190 1195 1200

Leu Val Thr Arg Pro Ile Ser Arg Gln Gln Val Arg Ser Gly Ala Ile
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Gly Asp Cys Leu Phe Glu Val Glu Trp His Arg Lys Ala Leu Leu Gly
 1220 1225 1230

Thr Thr Ala Gly Asp Asp Leu Ala Ile Val Gly Asp Gly Pro Ser Trp
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Pro Glu Ser Val Arg Ala Thr Ala Arg Phe Ala Thr Leu Asp Glu Phe
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Ala Ala Met Ser Ala Glu Glu Val Glu Gly Gly Ser Leu Pro Ser Arg
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Ala Gln Glu Ser Thr Ser Asp Leu Leu Ala Leu Val Gln Ser Trp Leu
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Ala Asp Glu Arg Phe Ala Glu Ser Gln Leu Val Val Val Thr Arg Ala
 1315 1320 1325

Ala Val Ser Ala Asp Ser Asp Ser Asp Val Ala Asp Leu Val Gly Ala
 1330 1335 1340

Ser Ser Trp Gly Leu Leu Ser Ser Ala Gln Ser Glu Asn Pro Gly Arg
 345 1350 1355 1360

Phe Val Leu Val Asp Val Asp Gly Thr Pro Glu Ser Trp Gln Ala Leu
 1365 1370 1375

Pro Ala Ala Val Arg Ala Gly Glu Pro Gln Leu Ala Leu Arg Arg Gly
 1380 1385 1390

Val Ala Leu Val Pro Arg Leu Ala Arg Leu Thr Val Arg Glu Glu Gly
 1395 1400 1405

Ser Ser Pro Gln Leu Asp Thr Asp Gly Thr Val Leu Ile Thr Gly Gly
 1410 1415 1420

Thr Gly Ala Leu Gly Gly Val Val Ala Arg His Leu Val Glu Glu His
 425 1430 1435 1440

Gly Ile Arg Arg Leu Val Leu Ala Gly Arg Arg Gly Trp Asn Ala Pro
 1445 1450 1455

Gly Val His Glu Leu Val Asp Glu Leu Ala Arg Ala Gly Ala Val Val
 1460 1465 1470

Glu Val Val Ala Cys Asp Val Ala Asp Arg Thr Asp Leu Glu His Val
 1475 1480 1485

Leu Ala Ala Ile Pro Val Asp Trp Pro Leu Arg Gly Ile Val His Thr
 1490 1495 1500

Ala Gly Val Leu Ala Asp Gly Val Ile Gly Ser Leu Ser Ala Ala Asp
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Val Gly Thr Val Phe Ala Pro Lys Val Thr Gly Ala Trp His Leu His
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 Glu Leu Thr Arg Asp Leu Asp Leu Ser Phe Phe Val Leu Phe Ser Ser
 1540 1545 1550
 Phe Ser Gly Ile Ala Gly Ala Ala Gly Gln Ala Asn Tyr Ala Ala Ala
 1555 1560 1565
 Asn Thr Phe Leu Asp Ala Leu Ala Arg Tyr Arg Arg Ala Arg Gly Leu
 1570 1575 1580
 Pro Gly Leu Ser Leu Ala Trp Gly Leu Trp Ala Gln Pro Ser Gly Met
 585 1590 1595 1600
 Thr Ser Gly Leu Asp Ala Ala Ser Val Glu Arg Leu Ala Arg Thr Gly
 1605 1610 1615
 Ile Ala Glu Leu Ser Thr Glu Asp Gly Leu Arg Leu Phe Asp Ala Ala
 1620 1625 1630
 Phe Ala Lys Asp Arg Ala Cys Val Val Ala Ala Arg Leu Asp Arg Ala
 1635 1640 1645
 Leu Leu Val Gly Asn Gly Arg Ser His Ala Ile Pro Ala Leu Leu Ser
 1650 1655 1660
 Ala Leu Val Pro Val Arg Gly Gly Val Ala Arg Lys Thr Ala Asn Ser
 665 1670 1675 1680
 Gln Ala Ala Asp Glu Asp Ala Leu Leu Gly Leu Val Arg Glu His Val
 1685 1690 1695
 Ser Ala Val Leu Gly Tyr Ser Gly Ala Val Glu Val Gly Gly Asp Arg
 1700 1705 1710
 Ala Phe Arg Asp Leu Gly Phe Asp Ser Leu Ser Gly Val Glu Leu Arg
 1715 1720 1725
 Asn Arg Leu Ala Gly Val Leu Gly Val Arg Leu Pro Ala Thr Ala Val
 1730 1735 1740
 Phe Asp Tyr Pro Thr Pro Arg Ala Leu Ala Arg Phe Leu His Gln Glu
 745 1750 1755 1760
 Leu Ala Gly Glu Val Ala Ser Thr Ser Thr Pro Val Thr Arg Ala Ala
 1765 1770 1775

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Ser Ala Glu Glu Asp Leu Val Ala Ile Val Gly Met Gly Cys Arg Phe
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 Pro Gly Gly Val Ser Ser Pro Glu Glu Leu Trp Arg Leu Val Ala Gly
 1795 1800 1805
 Gly Val Asp Ala Val Ala Gly Phe Pro Asp Asp Arg Gly Trp Asp Leu
 1810 1815 1820
 Ala Ala Leu Tyr Asp Pro Asp Pro Asp Arg Leu Gly Thr Ser Tyr Val
 825 1830 1835 1840
 Cys Glu Gly Gly Phe Leu Arg Asp Ala Ala Glu Phe Asp Ala Asp Met
 1845 1850 1855
 Phe Gly Ile Ser Pro Arg Glu Ala Leu Ala Met Asp Pro Gln Gln Arg
 1860 1865 1870
 Leu Leu Leu Glu Val Ala Trp Glu Thr Leu Glu Arg Ala Gly Ile Asp
 1875 1880 1885
 Pro Phe Ser Leu His Gly Ser Arg Thr Gly Val Phe Ala Gly Leu Met
 1890 1895 1900
 Tyr His Asp Tyr Gly Ala Arg Phe Ile Thr Arg Ala Pro Glu Gly Phe
 905 1910 1915 1920
 Glu Gly His Leu Gly Thr Gly Asn Ala Gly Ser Val Leu Ser Gly Arg
 1925 1930 1935
 Val Ala Tyr Ser Phe Gly Phe Glu Gly Pro Ala Val Thr Val Asp Thr
 1940 1945 1950
 Ala Cys Ser Ser Ser Leu Val Ala Leu His Leu Ala Gly Gln Ala Leu
 1955 1960 1965
 Arg Ala Gly Glu Cys Glu Phe Ala Leu Ala Gly Gly Val Thr Val Met
 1970 1975 1980
 Ser Thr Pro Thr Thr Phe Val Glu Phe Ser Arg Gln Arg Gly Leu Ala
 985 1990 1995 2000
 Pro Asp Gly Arg Cys Lys Ser Phe Ala Ala Ala Ala Asp Gly Thr Gly
 2005 2010 2015
 Trp Gly Glu Gly Ala Gly Leu Val Leu Leu Glu Arg Leu Ser Asp Ala
 2020 2025 2030

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Arg Arg Asn Gly His Glu Val Leu Ala Val Val Arg Gly Ser Ala Val
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Asn Gln Asp Gly Ala Ser Asn Gly Leu Thr Ala Pro Asn Gly Pro Ser
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Gln Gln Arg Val Ile Thr Gln Ala Leu Thr Ser Ala Gly Leu Ser Val
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Ser Asp Val Asp Ala Val Glu Ala His Gly Thr Gly Thr Arg Leu Gly
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Asp Pro Ile Glu Ala Gln Ala Leu Ile Ala Thr Tyr Gly Arg Asp Arg
 2100 2105 2110

Asp Pro Gly Arg Pro Leu Trp Leu Gly Ser Val Lys Ser Asn Ile Gly
 2115 2120 2125

His Thr Gln Ala Ala Ala Gly Val Ala Gly Val Ile Lys Met Val Met
 2130 2135 2140

Ala Met Arg Gln Gly Glu Leu Pro Arg Thr Leu His Val Asp Glu Pro
 2145 2150 2155 2160

Ser Ala Gln Val Asp Trp Ser Ala Gly Thr Val Gln Leu Leu Thr Glu
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Asn Thr Pro Trp Pro Asp Ser Gly Arg Leu Arg Arg Ala Gly Val Ser
 2180 2185 2190

Ser Phe Gly Ile Ser Gly Thr Asn Ala His Leu Ile Leu Glu Gln Pro
 2195 2200 2205

Pro Arg Glu Ser Gln Arg Ser Thr Glu Pro Asp Ser Gly Ser Val Arg
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Asp Phe Pro Val Val Pro Trp Met Val Ser Gly Lys Thr Pro Glu Ala
 2225 2230 2235 2240

Leu Ser Ala Gln Ala Asp Ala Leu Met Ser Tyr Leu Ser Asn Arg Val
 2245 2250 2255

Asp Ala Ser Pro Arg Asp Ile Gly Tyr Ser Leu Ala Val Thr Arg Pro
 2260 2265 2270

Ala Leu Asp His Arg Ala Val Val Leu Gly Ala Asp Arg Ala Ala Leu
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Leu Pro Gly Leu Lys Ala Leu Ala Val Ser Asn Asp Ala Ala Glu Val
 2290 2295 2300

Ile Thr Gly Thr Arg Ala Ala Gly Pro Val Gly Phe Val Phe Ser Gly
 305 2310 2315 2320

Gln Gly Gly Gln Trp Pro Gly Met Gly Ser Gly Leu His Ser Ala Phe
 2325 2330 2335

Pro Val Phe Ala Asp Ala Phe Asp Glu Ala Cys Cys Glu Leu Asp Ala
 2340 2345 2350

His Leu Gly Gln Met Ala Arg Leu Arg Asp Val Leu Ser Gly Ser Asp
 2355 2360 2365

Thr Gln Leu Leu Asp Gln Thr Leu Trp Ala Gln Pro Gly Leu Phe Ala
 2370 2375 2380

Leu Gln Val Gly Leu Trp Glu Leu Leu Gly Ser Trp Gly Val Arg Pro
 385 2390 2395 2400

Ala Val Val Leu Gly His Ser Val Gly Glu Leu Ala Ala Ala Phe Ala
 2405 2410 2415

Ala Gly Val Leu Ser Leu Arg Asp Ala Ala Arg Leu Val Ala Gly Arg
 2420 2425 2430

Ala Arg Leu Met Gln Ala Leu Pro Thr Gly Gly Ala Met Leu Ala Ala
 2435 2440 2445

Ala Ala Gly Glu Glu Gln Leu Arg Pro Leu Leu Ala Asp Cys Gly Asp
 2450 2455 2460

Arg Val Gly Ile Ala Ala Val Asn Ala Pro Gly Ser Val Val Leu Ser
 465 2470 2475 2480

Gly Asp Arg Asp Val Leu Asp Asp Ile Ala Gly Arg Leu Asp Gly Gln
 2485 2490 2495

Gly Ile Arg Ser Arg Trp Leu Arg Val Ser His Ala Phe His Ser His
 2500 2505 2510

Arg Met Asp Pro Met Leu Ala Glu Phe Thr Glu Ile Ala Arg Ser Val
 2515 2520 2525

Asp Tyr Arg Ser Ser Gly Leu Pro Ile Val Ser Thr Leu Thr Gly Glu
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Leu Asp Glu Val Gly Met Pro Ala Thr Pro Glu Tyr Trp Val Arg Gln
 545 2550 2555 2560

Val Arg Glu Pro Val Arg Phe Ala Asp Gly Val Ala Ala Leu Ala Ala
 2565 2570 2575

His Gly Val Ser Thr Val Val Glu Val Gly Pro Asp Gly Val Leu Ser
 2580 2585 2590

Ala Leu Val Gln Glu Cys Ala Ala Gly Ser Asp Gln Gly Gly Arg Val
 2595 2600 2605

Ala Ala Val Pro Leu Met Arg Ser Asn Arg Asp Glu Ala His Thr Val
 2610 2615 2620

Thr Thr Ala Leu Ala Gln Ile His Val Arg Gly Ala Glu Val Asp Trp
 625 2630 2635 2640

Arg Ser Phe Phe Ala Gly Thr Gly Ala Lys Gln Val Glu Leu Pro Thr
 2645 2650 2655

Tyr Ala Phe Gln Arg Gln Arg Tyr Trp Leu Asp Ser Pro Ser Glu Pro
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Val Gly Gln Ser Ala Asp Pro Ala Arg Gln Ser Gly Phe Trp Glu Leu
 2675 2680 2685

Val Glu Gln Glu Asp Val Ser Ala Leu Ser Ala Ala Leu His Ile Thr
 2690 2695 2700

Gly Asp His Asp Val Gln Ala Ser Leu Glu Ser Val Val Pro Val Leu
 705 2710 2715 2720

Ser Ser Trp His Arg Arg Ile Arg Asn Glu Ser Leu Val His Gln Trp
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Arg Tyr Arg Ile Ser Trp His Glu Arg Ala Asp Leu Pro Asp Pro Ser
 2740 2745 2750

Leu Ser Gly Thr Trp Leu Val Val Val Pro Glu Gly Trp Ser Ala Ser
 2755 2760 2765

Arg Gln Val Leu Arg Phe Asn Glu Met Phe Glu Glu Arg Gly Cys Pro
 2770 2775 2780

Ala Val Leu Phe Glu Leu Ala Gly His Asp Glu Glu Ala Leu Ala Gln
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Arg Phe Arg Ser Leu Pro Val Ala Ser Gly Gly Ile Ser Gly Val Leu
 2805 2810 2815

Ser Leu Leu Ala Leu Asp Glu Ser Pro Ser Ser Pro Asn Ala Ala Leu
 2820 2825 2830

Pro Asn Gly Ala Leu Asn Ser Leu Val Leu Leu Arg Ala Leu Arg Ala
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Ala Asp Val Ser Ala Pro Leu Trp Leu Ala Thr Cys Gly Gly Val Ala
 2850 2855 2860

Val Gly Asp Val Pro Val Asn Pro Gly Gln Ala Leu Val Trp Gly Leu
 865 2870 2875 2880

Gly Arg Val Val Gly Leu Glu His Pro Ala Trp Trp Gly Gly Leu Val
 2885 2890 2895

Asp Val Pro Cys Leu Leu Asp Glu Asp Ala Arg Glu Arg Leu Ser Val
 2900 2905 2910

Val Leu Ala Gly Leu Gly Glu Asp Glu Ile Ala Val Arg Pro Gly Gly
 2915 2920 2925

Val Phe Val Arg Arg Leu Glu Arg Ala Gly Ala Ala Ser Gly Ala Gly
 2930 2935 2940

Ser Val Trp Arg Pro Arg Gly Thr Val Leu Val Thr Gly Gly Thr Gly
 945 2950 2955 2960

Gly Leu Gly Ala His Val Ala Arg Trp Leu Ala Gly Ala Gly Ala Glu
 2965 2970 2975

His Val Val Leu Thr Ser Arg Arg Gly Ala Ala Ala Pro Gly Ala Gly
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Asp Leu Arg Ala Glu Leu Glu Ala Leu Gly Ala Arg Val Ser Ile Thr
 2995 3000 3005

Ala Cys Asp Val Ala Asp Arg Asp Ala Leu Ala Glu Val Leu Ala Thr
 3010 3015 3020

Ile Pro Asp Asp Cys Pro Leu Thr Ala Val Met His Ala Ala Gly Val
 025 3030 3035 3040

Val Glu Val Gly Asp Val Ala Ser Met Cys Leu Thr Asp Phe Val Gly
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Val Leu Ser Ala Lys Ala Gly Gly Ala Ala Asn Leu Asp Glu Leu Leu
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Ala Asp Val Glu Leu Asp Ala Phe Val Leu Phe Ser Ser Val Ser Gly
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Val Trp Gly Ala Gly Gly Gln Gly Ala Tyr Ala Ala Ala Asn Ala Tyr
 3090 3095 3100

Leu Asp Ala Leu Ala Gln Gln Arg Arg Ala Arg Gly Leu Val Gly Thr
 105 3110 3115 3120

Ala Val Ala Trp Gly Pro Trp Ala Gly Asp Gly Met Ala Ala Gly Glu
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Gly Gly Ala Gln Leu Arg Arg Ala Gly Leu Val Pro Met Ala Ala Asp
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Arg Ala Leu Leu Ala Leu Gln Gly Ala Leu Asp Arg Asp Glu Thr Ser
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Leu Val Val Ala Asp Met Ala Trp Glu Arg Phe Ala Pro Val Phe Ala
 3170 3175 3180

Met Ser Arg Arg Arg Pro Leu Leu Asp Glu Leu Pro Glu Ala Gln Gln
 185 3190 3195 3200

Ala Leu Ala Asp Ala Glu Asn Thr Thr Asp Ala Ala Asp Ser Ala Val
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Pro Leu Pro Arg Leu Ala Gly Met Ala Ala Ala Glu Arg Arg Arg Ala
 3220 3225 3230

Met Leu Asp Leu Val Leu Ala Glu Ala Ser Ile Val Leu Gly His Asn
 3235 3240 3245

Gly Ser Asp Pro Val Gly Pro Asp Arg Ala Phe Gln Glu Leu Gly Phe
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Asp Ser Leu Met Ala Val Glu Leu Arg Asn Arg Leu Gly Glu Ala Thr
 265 3270 3275 3280

Gly Leu Ser Leu Pro Ala Thr Leu Ile Phe Asp Tyr Pro Ser Pro Ser
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Ala Leu Ala Glu Gln Leu Val Gly Glu Leu Val Gly Ala Gln Pro Ala
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Thr Thr Val Val Ala Gly Ala Asp Pro Val Asp Asp Pro Val Val Val
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Val Ala Met Gly Cys Arg Tyr Pro Gly Asp Val Cys Ser Pro Glu Glu
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Leu Trp Gln Leu Val Ser Ala Gly Arg Asp Ala Val Ser Thr Phe Pro
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Val Asp Arg Gly Trp Asp Cys Asn Thr Leu Phe Asp Pro Asp Pro Asp
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Arg Ala Gly Ser Thr Tyr Val Arg Glu Gly Ala Phe Leu Thr Gly Ala
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Asp Arg Phe Asp Ala Gly Phe Phe Gly Ile Ser Pro Arg Glu Ala Arg
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Ala Met Asp Pro Gln Gln Arg Leu Leu Leu Glu Val Ala Trp Glu Val
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Phe Glu Arg Ala Gly Ile Ala Pro Leu Ser Leu Arg Gly Ser Arg Thr
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Gly Val Phe Ala Gly Thr Asn Gly Gln Asp His Gly Ala Lys Val Ala
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Ala Ala Pro Glu Ala Ala Gly His Leu Leu Thr Gly Asn Ala Ala Ser
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Val Leu Ala Gly Arg Leu Ser Tyr Thr Phe Gly Leu Glu Gly Pro Ala
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Val Ala Val Asp Thr Ala Cys Ser Ser Ser Leu Val Ala Leu His Leu
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Ala Cys Gln Ser Leu Arg Ser Gly Glu Cys Asp Met Ala Leu Ala Gly
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Gly Val Thr Val Met Ser Thr Pro Leu Ala Phe Leu Glu Phe Ser Arg
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Gln Arg Gly Leu Ala Pro Asp Gly Arg Cys Lys Ser Phe Ala Ala Ala
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Ala Asp Gly Thr Gly Trp Gly Glu Gly Ala Gly Leu Val Leu Leu Glu
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Arg Leu Ser Asp Ala Arg Arg Asn Gly His Arg Val Leu Ala Val Val
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Arg Gly Ser Ala Val Asn Gln Asp Gly Ala Ser Asn Gly Leu Thr Ala
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Pro Asn Gly Pro Ser Gln Gln Arg Val Ile Arg Gln Ala Leu Ala Asn
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Ala Gly Leu Ser Ala Ser Asp Val Asp Val Val Glu Ala His Gly Thr
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Gly Thr Gly Leu Gly Asp Pro Ile Glu Ala Gln Ala Leu Ile Ala Thr
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Tyr Gly Gln Glu Arg Asp Pro Glu Arg Ala Leu Trp Leu Gly Ser Ile
 3650 3655 3660

Lys Ser Asn Ile Gly His Thr Gln Ala Ala Ala Gly Val Ala Gly Val
 665 3670 3675 3680

Ile Lys Met Val Gln Ala Met Arg His Gly Glu Leu Pro Ala Thr Leu
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His Val Asp Lys Pro Thr Pro Gln Val Asp Trp Ser Ala Gly Ala Val
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Arg Leu Leu Thr Gly Asn Thr Pro Trp Pro Glu Ser Gly Arg Pro Arg
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Arg Ala Gly Val Ser Ser Phe Gly Ile Ser Gly Thr Asn Ala His Leu
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Ile Leu Glu Gln Pro Pro Ser Glu Pro Ala Glu Ile Asp Gln Ser Asp
 745 3750 3755 3760

Arg Arg Val Thr Ala His Pro Ala Val Ile Pro Trp Met Leu Ser Ala
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Arg Ser Leu Ala Ala Leu Gln Ala Gln Ala Ala Ala Leu Gln Ala Arg
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Leu Asp Arg Gly Pro Gly Ala Ser Pro Leu Asp Leu Gly Tyr Ser Leu
 3795 3800 3805

Ala Thr Thr Arg Ser Val Leu Asp Glu Arg Ala Val Val Trp Gly Ala
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 Thr Ala Pro Gly Val Ile Thr Gly Ser Ala Asn Ser Gly Gly Arg Ile
 3845 3850 3855
 Gly Phe Val Phe Ser Gly Gln Gly Ser Gln Trp Leu Gly Met Gly Lys
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 Ala Leu Cys Ala Ala Phe Pro Ala Phe Ala Asp Ala Phe Glu Glu Ala
 3875 3880 3885
 Cys Asp Ala Leu Ser Ala His Leu Gly Ala Asp Val Arg Gly Val Leu
 3890 3895 3900
 Phe Gly Ala Asp Glu Gln Met Leu Asp Arg Thr Leu Trp Ala Gln Ser
 905 3910 3915 3920
 Gly Ile Phe Ala Val Gln Val Gly Leu Leu Gly Leu Leu Arg Ser Trp
 3925 3930 3935
 Gly Val Arg Pro Ala Ala Val Leu Gly His Ser Val Gly Glu Leu Ala
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 Val Ala Ala Arg Ala His Leu Met Gln Ala Leu Pro Thr Gly Gly Ala
 3970 3975 3980
 Met Leu Ala Val Ala Thr Ser Glu Ala Ala Val Gly Pro Leu Leu Ser
 985 3990 3995 4000
 Gly Val Cys Asp Arg Val Ser Ile Ala Ala Ile Asn Gly Pro Glu Ser
 4005 4010 4015
 Val Val Leu Ser Gly Asp Arg Asp Val Leu Val Glu Leu Ala Gly Glu
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 Phe Asp Ala Arg Gly Leu Arg Thr Lys Trp Leu Arg Val Ser His Ala
 4035 4040 4045
 Phe His Ser His Arg Met Glu Pro Ile Leu Asp Glu Tyr Ala Glu Thr
 4050 4055 4060
 Ala Arg Cys Val Glu Phe Gly Glu Pro Val Val Pro Ile Val Ser Ala
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Trp Thr Arg Gln Val Arg Asp Pro Val Arg Phe Gly Asp Gly Val Arg
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Ala Leu Val Gly Gln Gly Val Asp Thr Ile Val Glu Phe Gly Pro Asp
4115 4120 4125

Gly Ala Leu Ser Ala Leu Val Glu Gln Cys Leu Ala Gly Ser Asp Gln
4130 4135 4140

Ala Gly Arg Val Ala Ala Ile Pro Leu Met Arg Arg Asp Arg Asp Glu
145 4150 4155 4160

Val Glu Thr Ala Val Ala Ala Leu Ala His Val His Val Arg Gly Gly
4165 4170 4175

Ala Val Asp Trp Ser Ala Cys Phe Ala Gly Thr Gly Ala Arg Thr Val
4180 4185 4190

Glu Leu Pro Thr Tyr Ala Phe Gln Arg Gln Arg Tyr Trp Leu Ala Gly
4195 4200 4205

Gln Ala Asp Gly Arg Gly Gly Asp Val Val Ala Asp Pro Val Asp Ala
4210 4215 4220

Arg Phe Trp Glu Leu Val Glu Arg Ala Asp Pro Glu Pro Leu Val Asp
225 4230 4235 4240

Glu Leu Cys Ile Asp Arg Asp Gln Pro Phe Arg Glu Val Leu Pro Val
4245 4250 4255

Leu Ala Ser Trp Arg Glu Lys Gln Arg Gln Glu Ala Leu Ala Asp Ser
4260 4265 4270

Trp Arg Tyr Gln Val Arg Trp Arg Ser Val Glu Val Pro Ser Ala Ala
4275 4280 4285

Ala Leu Arg Gly Val Trp Leu Val Val Leu Pro Ala Asp Val Pro Arg
4290 4295 4300

Asp Gln Pro Ala Val Val Ile Asp Ala Leu Ile Ala Arg Gly Ala Glu
305 4310 4315 4320

Val Ala Val Leu Glu Leu Thr Glu Gln Asp Leu Gln Arg Ser Ala Leu
4325 4330 4335

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Val Asp Lys Val Arg Ala Val Ile Ala Asp Arg Thr Glu Val Thr Gly
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 Val Leu Ser Leu Leu Ala Met Asp Gly Met Pro Cys Ala Ala His Pro
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 His Leu Ser Arg Gly Val Ala Ala Thr Val Ile Leu Thr Gln Val Leu
 4370 4375 4380
 Gly Asp Ala Gly Val Ser Ala Pro Leu Trp Leu Ala Thr Thr Gly Gly
 385 4390 4395 4400
 Val Glu Ala Gly Thr Glu Asp Gly Pro Ala Asp Pro Asp His Gly Leu
 4405 4410 4415
 Ile Trp Gly Leu Gly Arg Val Val Gly Leu Glu His Pro Gln Trp Trp
 4420 4425 4430
 Gly Gly Leu Ile Asp Leu Pro Glu Thr Leu Asp Glu Thr Ser Arg Asn
 4435 4440 4445
 Gly Leu Val Ala Ala Leu Ala Gly Thr Ala Ala Glu Asp Gln Leu Ala
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 Val Arg Ser Ser Gly Leu Phe Val Arg Arg Val Val Arg Ala Ala Arg
 4465 4470 4475 4480
 Asn Pro Arg Ser Glu Thr Trp Arg Ser Arg Gly Thr Val Leu Ile Thr
 4485 4490 4495
 Gly Gly Thr Gly Ala Leu Gly Ala Glu Val Ala Arg Trp Leu Ala Arg
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 Arg Gly Ala Glu His Leu Val Leu Ile Ser Arg Arg Gly Pro Glu Ala
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 Pro Gly Ala Ala Asp Leu Gly Ala Glu Leu Thr Glu Leu Gly Val Lys
 4530 4535 4540
 Val Thr Val Leu Ala Cys Asp Val Thr Asp Arg Asp Glu Leu Ala Ala
 4545 4550 4555 4560
 Val Leu Ala Ala Val Pro Thr Glu Tyr Pro Leu Ser Ala Val Val His
 4565 4570 4575
 Thr Ala Gly Val Gly Thr Pro Ala Asn Leu Ala Glu Thr Thr Leu Ala
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Gln Phe Ala Asp Val Leu Ser Ala Lys Val Val Gly Ala Ala Asn Leu
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Asp Arg Leu Leu Gly Gly Gln Pro Leu Asp Ala Phe Val Leu Phe Ser
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Ser Ile Ser Gly Val Trp Gly Ala Gly Gly Gln Gly Ala Tyr Ser Ala
 625 4630 4635 4640

Ala Asn Ala Tyr Leu Asp Ala Leu Ala Glu Arg Arg Arg Ala Cys Gly
 4645 4650 4655

Arg Pro Ala Thr Cys Ile Ala Trp Gly Pro Trp Ala Gly Ala Gly Met
 4660 4665 4670

Ala Val Gln Glu Gly Asn Glu Ala His Leu Arg Arg Arg Gly Leu Val
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Pro Met Glu Pro Gln Ser Ala Leu Phe Ala Leu Gln Gln Ala Leu Ser
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Gln Arg Glu Thr Ala Ile Thr Val Ala Asp Val Asp Trp Glu Arg Phe
 705 4710 4715 4720

Ala Ala Ser Phe Thr Ala Ala Arg Pro Arg Pro Leu Leu Glu Glu Ile
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Val Asp Leu Arg Pro Asp Thr Glu Thr Glu Glu Lys His Gly Ala Gly
 4740 4745 4750

Glu Leu Gly Gln Gln Leu Ala Ala Leu Pro Pro Ala Glu Arg Gly His
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Leu Leu Leu Glu Val Val Leu Ala Glu Thr Ala Ser Thr Leu Gly His
 4770 4775 4780

Asp Ser Ala Glu Ala Val Gln Pro Asp Arg Thr Phe Ala Glu Leu Gly
 785 4790 4795 4800

Phe Asp Ser Leu Thr Ala Val Glu Leu Arg Asn Arg Leu Asn Ala Val
 4805 4810 4815

Thr Gly Leu Arg Leu Pro Pro Thr Leu Val Phe Asp His Pro Thr Pro
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Leu Ala Leu Ser Glu Gln Leu Val Pro Ala Leu Val Ala Glu Pro Asp
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Asn Gly Ile Glu Ser Leu Leu Ala Glu Leu Asp Arg Leu Asp Thr Thr
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 Glu Leu Glu Glu Ala His Glu Arg Leu His Glu Leu Glu Arg Gln Glu
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 His Asp Pro Ile Ala Ile Val Ser Met Gly Cys Arg Tyr Pro Gly Gly
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Arg Val Ala Tyr Ser Phe Gly Phe Glu Gly Pro Ala Val Thr Val Asp	
1940 1945 1950	
acg gcg tgt tcg tcg tcg ttg gtg gcg ctg cac ctg gcg ggt caa gca	5904
Thr Ala Cys Ser Ser Ser Leu Val Ala Leu His Leu Ala Gly Gln Ala	
1955 1960 1965	
ctg cgg tct ggt gag tgt gat ctg gct ctt gcg ggt ggt gtg acg gtg	5952
Leu Arg Ser Gly Glu Cys Asp Leu Ala Leu Ala Gly Gly Val Thr Val	
1970 1975 1980	
atg gcc acg ccg ggg atg ttc gtg gag ttt tcg cgt caa cgg ggc ttg	6000
Met Ala Thr Pro Gly Met Phe Val Glu Phe Ser Arg Gln Arg Gly Leu	
1985 1990 1995 2000	

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Gly Trp Gly Glu Gly Ala Gly Leu Val Leu Leu Glu Arg Leu Ser Asp	
2020 2025 2030	
gcc cgg cgc aac ggg cac gcg gtt ctg gcg gtc gtg cgg ggt agc gcg	6144
Ala Arg Arg Asn Gly His Ala Val Leu Ala Val Val Arg Gly Ser Ala	
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Val Asn Gln Asp Gly Ala Ser Asn Gly Leu Thr Ala Pro Asn Gly Pro	
2050 2055 2060	
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Ser Gln Gln Arg Val Ile Thr Gln Ala Leu Ala Ser Ala Gly Leu Ser	
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Val Ser Asp Val Asp Ala Val Glu Ala His Gly Thr Gly Thr Arg Leu	
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Gly Asp Pro Ile Glu Ala Gln Ala Leu Ile Ala Thr Tyr Gly Gln Gly	
2100 2105 2110	
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Arg Asp Ser Asp Arg Pro Leu Trp Leu Gly Ser Val Lys Ser Asn Ile	
2115 2120 2125	
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Gly His Thr Gln Ala Ala Ala Gly Val Ala Gly Val Ile Lys Met Val	
2130 2135 2140	
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Met Ala Met Arg His Gly Gln Leu Pro Ala Thr Leu His Val Asp Glu	
2145 2150 2155 2160	
cct acg tcg gaa gtg gat tgg tcg gcg ggg gat gtc cag ctc ctc acg	6528
Pro Thr Ser Glu Val Asp Trp Ser Ala Gly Asp Val Gln Leu Leu Thr	
2165 2170 2175	
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Ala Ser Lys Thr Pro Asp Glu Thr Ala Asp Lys Ser Gly Pro Asp Ser	
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Glu Ser Thr Val Asp Leu Pro Ala Val Pro Leu Ile Val Ser Gly Arg	
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Thr Pro Ala Ala Leu Ser Ala Gln Ala Ser Ala Leu Leu Ser Tyr Leu	
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Ser Ser Arg Ala Ala Leu Glu Glu Arg Ala Val Val Leu Gly Ala Asp	
2275 2280 2285	
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Arg Glu Thr Leu Leu Ser Gly Leu Glu Ala Leu Ala Ser Gly Arg Glu	
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Ala Ser Gly Val Val Ser Gly Ser Pro Val Ser Gly Gly Val Gly Phe	
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Val Phe Ala Gly Gln Gly Gly Gln Trp Leu Gly Met Gly Arg Gly Leu	
2325 2330 2335	
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Tyr Ser Val Phe Pro Val Phe Ala Asp Ala Phe Asp Glu Ala Cys Ala	
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Gly Leu Asp Ala His Leu Gly Gln Asp Val Gly Val Arg Asp Val Val	
2355 2360 2365	
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Phe Gly Ser Asp Gly Ser Leu Leu Asp Arg Thr Leu Trp Ala Gln Ser	
2370 2375 2380	

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Ala Ala Val Ala Ala Gly Val Leu Ser Leu Pro Asp Ala Ala Arg Met	
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Val Ala Gly Arg Ala Arg Leu Met Gln Ala Leu Pro Ser Gly Gly Ala	
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Met Leu Ala Val Ala Ala Gly Glu Glu Gln Leu Arg Pro Leu Leu Ala	
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Val Val Leu Ser Gly Asp Arg Glu Val Leu Asp Asp Ile Ala Gly Ala	
2485 2490 2495	
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Leu Asp Gly Gln Gly Ile Arg Trp Arg Arg Leu Arg Val Ser His Ala	
2500 2505 2510	
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Phe His Ser Tyr Arg Met Asp Pro Met Leu Gln Glu Phe Ala Glu Ile	
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Ala Arg Ser Val Asp Tyr Arg Arg Gly Asp Leu Pro Val Val Ser Thr	
2530 2535 2540	
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Leu Thr Gly Glu Leu Asp Thr Ala Gly Val Met Ala Thr Pro Glu Tyr	
2545 2550 2555 2560	
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2565 2570 2575	

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Ala Thr Leu Ser Ala Leu Ile Pro Asp Cys His Ser Trp Ala Asp Gln	
2595 2600 2605	
gcc atg ccg att ccg atg ctg cgt aaa gac cgt acg gaa acc gaa act	7872
Ala Met Pro Ile Pro Met Leu Arg Lys Asp Arg Thr Glu Thr Glu Thr	
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Val Val Ala Ala Val Ala Arg Ala His Thr Arg Gly Val Pro Val Glu	
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Trp Ser Ala Tyr Phe Ala Gly Thr Gly Ala Arg Arg Val Glu Leu Pro	
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Thr Tyr Ala Phe Gln Arg Gln Arg Tyr Trp Leu Glu Thr Ser Asp Tyr	
2660 2665 2670	
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Gly Asp Val Thr Gly Ile Gly Leu Ala Ala Ala Glu His Pro Leu Leu	
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Gly Ala Val Val Ala Leu Ala Asp Gly Asp Gly Met Val Leu Thr Gly	
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Arg Leu Ser Val Gly Thr His Pro Trp Leu Ala Gln His Arg Val Leu	
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Gly Glu Val Val Val Pro Gly Thr Ala Ile Leu Glu Met Ala Leu His	
2725 2730 2735	
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Ala Gly Ala Arg Leu Gly Cys Asp Arg Val Glu Glu Leu Thr Leu Glu	
2740 2745 2750	
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Thr Pro Leu Val Val Pro Glu Arg Ala Ala Gly Ala Gly Ser Arg Gly	
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Arg Thr Asn Asp Ala Ile Glu Ile Gln Leu Leu Val Asn Ala Pro Asp	
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Glu Gly Gly Arg Arg Arg Val Ser Leu Tyr Ser Arg Pro Ala Gly Gly	
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Phe Glu Tyr Gly Pro Leu Phe Gln Gly Leu Gln Ala Ala Trp Arg Arg	
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Gln Ala Ser Ala Leu Gly Asp Arg Pro Glu Gln Gly Gly Ala Trp Leu	
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Pro Phe Ser Phe Thr Gly Val Glu Leu Ser Ala Pro Ala Gly Thr Ile	
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Leu Arg Ser Val Ser Ser Gly Gln Leu Ala Asn Arg Asp Ala Val Arg	
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Asp Ala Leu Phe Glu Val Thr Trp Glu Pro Val Ala Thr Gln Ser Thr	
2995 3000 3005	
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Glu Pro Gly Arg Trp Ala Leu Leu Gly Asp Thr Ala Cys Gly Lys Asp	
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Val Val Tyr Cys Ala Gly Glu Gln Ala Asp Pro Gly Thr Gly Ala Ala	
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Ala Leu Ala Glu Thr Gln Gln Thr Leu Ala Leu Leu Gln Ala Trp Leu	
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Ala Glu Pro Arg Leu Ala Glu Ala Arg Leu Val Val Val Thr Cys Ala	
3090 3095 3100	
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Ala Val Thr Thr Ala Pro Ser Asp Gly Ala Ser Glu Leu Ala His Ala	
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Pro Leu Trp Gly Leu Leu Arg Ala Ala Gln Val Glu Asn Pro Gly Gln	
3125 3130 3135	
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Val Gly Ala Val Phe Gly Pro Lys Ala Ala Gly Ala Trp Asn Leu His	
3300 3305 3310	
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Glu Leu Thr Arg Asp Thr Asp Leu Ser Phe Phe Ala Leu Phe Ser Ser	
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Val Leu Gly Tyr Ser Ser Ala Ala Asp Val Gly Val Glu Arg Ala Phe	
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Arg Asp Leu Gly Phe Asp Ser Leu Ser Gly Val Glu Leu Arg Asn Arg	
3490 3495 3500	
ctt gcc ggg gtg ctg ggg gtg cgg ttg ccg gcg act gcg gtg ttc gac	10560
Leu Ala Gly Val Leu Gly Val Arg Leu Pro Ala Thr Ala Val Phe Asp	
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Tyr Pro Thr Pro Arg Ala Leu Ala Arg Phe Leu His Gln Glu Leu Ala	
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Val Ala Glu Asp Asp Leu Val Ala Ile Val Gly Met Gly Cys Arg Phe	
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Pro Gly Gln Val Ser Ser Pro Glu Glu Leu Trp Arg Leu Val Ala Gly	
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3635 3640 3645	
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Pro Gly Ser Leu Arg Gly Ser Arg Thr Gly Val Phe Ala Gly Leu Met	
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Tyr His Asp Tyr Gly Ala Arg Phe Ala Ser Arg Ala Pro Glu Gly Phe	
3685 3690 3695	
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Glu Gly Tyr Leu Gly Asn Gly Ser Ala Gly Ser Val Ala Ser Gly Arg	
3700 3705 3710	
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Ile Ala Tyr Ser Phe Gly Phe Glu Gly Pro Ala Val Thr Val Asp Thr	
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Arg Ser Gly Glu Cys Asp Leu Ala Leu Ala Gly Gly Val Thr Val Met	
3745 3750 3755 3760	
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Ser Thr Pro Gly Thr Phe Val Glu Phe Ser Arg Gln Arg Gly Leu Ala	
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Gln Gln Arg Val Ile Gln Gln Ala Leu Ala Ser Ala Gly Leu Ser Val	
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 Gly Phe Leu Arg Gly Val Ala Asp Phe Asp Ala Gly Leu Phe Gly Ile
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Gly Lys Thr Glu Thr Ala Leu Arg Glu Gln Ala Ala Glu Leu Leu Ser
 485 490 495

Val Val Thr Glu His Pro Glu Pro Gly Leu Gly Asp Val Gly Tyr Ser
 500 505 510

Leu Ala Thr Gly Arg Ala Ala Met Glu His Arg Ala Val Val Val Ala
 515 520 525

Asp Asp Arg Asp Ser Phe Val Ala Gly Leu Thr Ala Leu Ala Ala Gly
 530 535 540

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Val	Pro	Ala	Ala	Asn	Val	Val	Gln	Gly	Ala	Ala	Asp	Cys	Lys	Gly	Lys	545	550	555	560
Val	Ala	Phe	Val	Phe	Pro	Gly	Gln	Gly	Ser	His	Trp	Gln	Gly	Met	Ala	565	570	575	
Arg	Glu	Leu	Ser	Glu	Ser	Ser	Pro	Val	Phe	Arg	Arg	Lys	Leu	Ala	Glu	580	585	590	
Cys	Ala	Ala	Ala	Thr	Ala	Pro	Tyr	Val	Asp	Trp	Ser	Leu	Leu	Gly	Val	595	600	605	
Leu	Arg	Gly	Asp	Pro	Asp	Ala	Pro	Ala	Leu	Asp	Arg	Asp	Asp	Val	Ile	610	615	620	
Gln	Leu	Ala	Leu	Phe	Ala	Met	Met	Val	Ser	Leu	Ala	Glu	Leu	Trp	Arg	625	630	635	640
Ser	Cys	Gly	Val	Glu	Pro	Ala	Ala	Val	Val	Gly	His	Ser	Gln	Gly	Glu	645	650	655	
Ile	Ala	Ala	Ala	His	Val	Ala	Gly	Ala	Leu	Ser	Leu	Thr	Asp	Ala	Val	660	665	670	
Arg	Ile	Ile	Ala	Ala	Arg	Cys	Asp	Ala	Val	Ser	Ala	Leu	Thr	Gly	Lys	675	680	685	
Gly	Gly	Met	Leu	Ala	Ile	Ala	Leu	Pro	Glu	Ser	Ala	Val	Val	Lys	Arg	690	695	700	
Ile	Ala	Gly	Leu	Pro	Glu	Leu	Thr	Val	Ala	Ala	Val	Asn	Gly	Pro	Gly	705	710	715	720
Ser	Thr	Val	Val	Ser	Gly	Glu	Pro	Ser	Ala	Leu	Glu	Arg	Leu	Gln	Thr	725	730	735	
Glu	Leu	Thr	Ala	Glu	Asn	Val	Gln	Thr	Arg	Arg	Val	Gly	Ile	Asp	Tyr	740	745	750	
Ala	Ser	His	Ser	Pro	Gln	Ile	Ala	Gln	Val	Gln	Gly	Arg	Leu	Leu	Asp	755	760	765	
Arg	Leu	Gly	Glu	Val	Gly	Ser	Glu	Pro	Ala	Glu	Ile	Ala	Phe	Tyr	Ser	770	775	780	
Thr	Val	Thr	Gly	Glu	Arg	Thr	Asp	Thr	Gly	Arg	Leu	Asp	Ala	Asp	Tyr	785	790	795	800

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Trp	Tyr	Gln	Asn	Leu	Arg	Gln	Pro	Val	Arg	Phe	Gln	Gln	Thr	Val	Ala		
				805					810					815			
Arg	Met	Ala	Asp	Gln	Gly	Tyr	Arg	Phe	Phe	Val	Glu	Val	Ser	Pro	His		
			820					825					830				
Pro	Leu	Leu	Thr	Ala	Gly	Ile	Gln	Glu	Thr	Leu	Glu	Ala	Ala	Asp	Ala		
			835					840					845				
Gly	Gly	Val	Val	Val	Gly	Ser	Leu	Arg	Arg	Gly	Glu	Gly	Gly	Ser	Arg		
		850					855				860						
Arg	Trp	Leu	Thr	Ser	Leu	Ala	Glu	Cys	Gln	Val	Arg	Gly	Leu	Pro	Val		
865					870					875					880		
Asn	Trp	Glu	Gln	Val	Phe	Leu	Asn	Thr	Gly	Ala	Arg	Arg	Val	Pro	Leu		
				885					890					895			
Pro	Thr	Tyr	Pro	Phe	Gln	Arg	Gln	Arg	Tyr	Trp	Leu	Glu	Ser	Ala	Glu		
			900					905					910				
Tyr	Asp	Ala	Gly	Asp	Leu	Gly	Ser	Val	Gly	Leu	Leu	Ser	Ala	Glu	His		
		915					920					925					
Pro	Leu	Leu	Gly	Ala	Ala	Val	Thr	Leu	Ala	Asp	Ala	Gly	Gly	Phe	Leu		
		930					935					940					
Leu	Thr	Gly	Lys	Leu	Ser	Val	Lys	Thr	Gln	Pro	Trp	Leu	Ala	Asp	His		
945					950					955					960		
Val	Val	Gly	Gly	Ala	Ile	Leu	Leu	Pro	Gly	Thr	Ala	Phe	Val	Glu	Met		
				965					970					975			
Leu	Ile	Arg	Ala	Ala	Asp	Gln	Val	Gly	Cys	Asp	Leu	Ile	Glu	Glu	Leu		
			980					985					990				
Ser	Leu	Thr	Thr	Pro	Leu	Val	Leu	Pro	Ala	Thr	Gly	Ala	Val	Gln	Val		
		995					1000					1005					
Gln	Ile	Ala	Val	Gly	Gly	Pro	Asp	Glu	Ala	Gly	Arg	Arg	Ser	Val	Arg		
		1010				1015					1020						
Val	His	Ser	Cys	Arg	Asp	Asp	Ala	Val	Pro	Gln	Asp	Ser	Trp	Thr	Cys		
025					1030					1035				1040			
His	Ala	Thr	Gly	Thr	Leu	Thr	Ser	Ser	Asp	His	Gln	Asp	Ala	Gly	Gln		
				1045					1050					1055			

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Gly Pro Asp Gly Ile Trp Pro Pro Asn Asp Ala Val Ala Val Pro Leu
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Asp Ser Phe Tyr Ala Arg Ala Ala Glu Arg Gly Phe Asp Phe Gly Pro
 1075 1080 1085

Ala Phe Gln Gly Leu Gln Ala Ala Trp Lys Arg Gly Asp Glu Ile Phe
 1090 1095 1100

Ala Glu Val Gly Leu Pro Thr Ala His Arg Glu Asp Ala Gly Arg Phe
 1105 1110 1115 1120

Gly Ile His Pro Ala Leu Leu Asp Ala Ala Leu Gln Ala Leu Gly Ala
 1125 1130 1135

Ala Glu Glu Asp Pro Asp Glu Gly Trp Leu Pro Phe Ala Trp Gln Gly
 1140 1145 1150

Val Ser Leu Lys Ala Thr Gly Ala Leu Ser Leu Arg Val His Leu Val
 1155 1160 1165

Pro Ala Gly Ala Asn Ala Val Ser Val Phe Thr Thr Asp Thr Thr Gly
 1170 1175 1180

Gln Ala Val Leu Ser Ile Asp Ser Leu Val Leu Arg Gln Ile Ser Asp
 1185 1190 1195 1200

Lys Gln Leu Ala Ala Ala Arg Ala Met Glu His Glu Ser Leu Phe Arg
 1205 1210 1215

Val Asp Trp Lys Arg Ile Ser Pro Gly Ala Ala Lys Pro Val Ser Trp
 1220 1225 1230

Ala Val Ile Gly Asn Asp Glu Leu Ala Arg Ala Cys Gly Ser Ala Leu
 1235 1240 1245

Gly Thr Glu Leu His Pro Asp Leu Thr Gly Leu Ala Asp Pro Pro Pro
 1250 1255 1260

Asp Val Val Val Val Pro Cys Gly Ala Ser Arg Gln Asp Leu Asp Val
 1265 1270 1275 1280

Ala Ser Glu Ala Arg Ala Ala Thr Gln Arg Met Leu Asp Leu Ile Gln
 1285 1290 1295

Asp Trp Leu Ala Ala Ala Arg Phe Ala Gly Ser Arg Leu Val Val Val
 1300 1305 1310

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Thr Cys Gly Ala Ala Ser Thr Gly Pro Ala Glu Gly Val Ser Asp Leu
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Val His Ala Ala Ser Trp Gly Leu Leu Arg Ser Ala Gln Ser Glu Asn
 1330 1335 1340

Pro Asp Arg Phe Val Leu Val Asp Val Asp Gly Thr Ala Glu Ser Trp
 1345 1350 1355 1360

Arg Ala Leu Ala Ala Ala Val Arg Ser Gly Glu Pro Gln Leu Ala Leu
 1365 1370 1375

Arg Ala Gly Glu Val Arg Val Pro Arg Leu Ala Arg Cys Val Ala Ala
 1380 1385 1390

Glu Asp Ser Arg Ile Pro Val Pro Gly Ala Asp Gly Thr Val Leu Ile
 1395 1400 1405

Ser Gly Gly Thr Gly Leu Leu Gly Gly Leu Val Ala Arg His Leu Val
 1410 1415 1420

Ala Glu Arg Gly Val Arg Arg Leu Val Leu Ala Gly Arg Arg Gly Trp
 1425 1430 1435 1440

Ser Ala Pro Gly Val Thr Asp Leu Val Asp Glu Leu Val Gly Leu Gly
 1445 1450 1455

Ala Ala Val Glu Val Ala Ser Cys Asp Val Gly Asp Arg Ala Gln Leu
 1460 1465 1470

Asp Arg Leu Leu Thr Thr Ile Ser Ala Glu Phe Pro Leu Arg Gly Val
 1475 1480 1485

Val His Ala Ala Gly Ala Leu Ala Asp Gly Val Val Glu Ser Leu Thr
 1490 1495 1500

Pro Glu His Val Ala Lys Val Phe Gly Pro Lys Ala Ala Gly Ala Trp
 1505 1510 1515 1520

His Leu His Glu Leu Thr Leu Asp Leu Asp Leu Ser Phe Phe Val Leu
 1525 1530 1535

Phe Ser Ser Phe Ser Gly Val Ala Gly Ala Ala Gly Gln Gly Asn Tyr
 1540 1545 1550

Ala Ala Ala Asn Ala Phe Leu Asp Gly Leu Ala Gln His Arg Arg Thr
 1555 1560 1565

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Ala Gly Leu Pro Ala Val Ser Leu Ala Trp Gly Leu Trp Glu Gln Pro
 1570 1575 1580

Ser Gly Met Thr Gly Ala Leu Asp Ala Ala Gly Arg Ser Arg Ile Ala
 585 1590 1595 1600

Arg Thr Asn Pro Pro Met Ser Ala Pro Asp Gly Leu Arg Leu Phe Glu
 1605 1610 1615

Met Ala Phe Arg Val Pro Gly Glu Ser Leu Leu Val Pro Val His Val
 1620 1625 1630

Asp Leu Asn Ala Leu Arg Ala Asp Ala Ala Asp Gly Gly Val Pro Ala
 1635 1640 1645

Leu Leu Arg Asp Leu Val Pro Ala Pro Val Arg Arg Ser Ala Val Asn
 1650 1655 1660

Glu Ser Ala Asp Val Asn Gly Leu Val Gly Arg Leu Arg Arg Leu Pro
 665 1670 1675 1680

Asp Leu Asp Gln Glu Thr Gln Leu Leu Gly Leu Val Arg Glu His Val
 1685 1690 1695

Ser Ala Val Leu Gly His Ser Gly Ala Val Glu Val Gly Ala Asp Arg
 1700 1705 1710

Ala Phe Arg Asp Leu Gly Phe Asp Ser Leu Ser Gly Val Glu Phe Arg
 1715 1720 1725

Asn Arg Leu Gly Gly Val Leu Gly Val Arg Leu Pro Ala Thr Ala Val
 1730 1735 1740

Phe Asp Tyr Pro Thr Pro Arg Ala Leu Val Arg Phe Leu Leu Asp Lys
 745 1750 1755 1760

Leu Ile Gly Gly Val Glu Ala Pro Thr Pro Ala Pro Ala Ala Val Ala
 1765 1770 1775

Ala Val Thr Ala Asp Asp Pro Val Val Ile Val Gly Met Gly Cys Arg
 1780 1785 1790

Tyr Pro Gly Gly Val Ser Ser Pro Glu Glu Leu Trp Arg Leu Val Ala
 1795 1800 1805

Gly Gly Leu Asp Ala Val Ala Glu Phe Pro Asp Asp Arg Gly Trp Asp
 1810 1815 1820

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Gln Ala Gly Leu Phe Asp Pro Asp Pro Asp Arg Leu Gly Thr Ser Tyr
 825 1830 1835 1840

Val Cys Glu Gly Gly Phe Leu Arg Asp Ala Ala Glu Phe Asp Ala Gly
 1845 1850 1855

Phe Phe Gly Ile Ser Pro Arg Glu Ala Leu Ala Met Asp Pro Gln Gln
 1860 1865 1870

Arg Leu Leu Leu Glu Val Ala Trp Glu Thr Val Glu Arg Ala Gly Ile
 1875 1880 1885

Asp Pro Leu Ser Leu Arg Gly Ser Arg Thr Gly Val Phe Ala Gly Leu
 1890 1895 1900

Met His His Asp Tyr Gly Ala Arg Phe Ile Thr Arg Ala Pro Glu Gly
 905 1910 1915 1920

Phe Glu Gly Tyr Leu Gly Asn Gly Ser Ala Gly Gly Val Phe Ser Gly
 1925 1930 1935

Arg Val Ala Tyr Ser Phe Gly Phe Glu Gly Pro Ala Val Thr Val Asp
 1940 1945 1950

Thr Ala Cys Ser Ser Ser Leu Val Ala Leu His Leu Ala Gly Gln Ala
 1955 1960 1965

Leu Arg Ser Gly Glu Cys Asp Leu Ala Leu Ala Gly Gly Val Thr Val
 1970 1975 1980

Met Ala Thr Pro Gly Met Phe Val Glu Phe Ser Arg Gln Arg Gly Leu
 985 1990 1995 2000

Ala Ala Asp Gly Arg Cys Lys Ser Phe Ala Ala Ala Ala Asp Gly Thr
 2005 2010 2015

Gly Trp Gly Glu Gly Ala Gly Leu Val Leu Leu Glu Arg Leu Ser Asp
 2020 2025 2030

Ala Arg Arg Asn Gly His Ala Val Leu Ala Val Val Arg Gly Ser Ala
 2035 2040 2045

Val Asn Gln Asp Gly Ala Ser Asn Gly Leu Thr Ala Pro Asn Gly Pro
 2050 2055 2060

Ser Gln Gln Arg Val Ile Thr Gln Ala Leu Ala Ser Ala Gly Leu Ser
 065 2070 2075 2080

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Val Ser Asp Val Asp Ala Val Glu Ala His Gly Thr Gly Thr Arg Leu
 2085 2090 2095
 Gly Asp Pro Ile Glu Ala Gln Ala Leu Ile Ala Thr Tyr Gly Gln Gly
 2100 2105 2110
 Arg Asp Ser Asp Arg Pro Leu Trp Leu Gly Ser Val Lys Ser Asn Ile
 2115 2120 2125
 Gly His Thr Gln Ala Ala Ala Gly Val Ala Gly Val Ile Lys Met Val
 2130 2135 2140
 Met Ala Met Arg His Gly Gln Leu Pro Ala Thr Leu His Val Asp Glu
 145 2150 2155 2160
 Pro Thr Ser Glu Val Asp Trp Ser Ala Gly Asp Val Gln Leu Leu Thr
 2165 2170 2175
 Glu Asn Thr Pro Trp Pro Gly Asn Ser His Pro Arg Arg Val Gly Val
 2180 2185 2190
 Ser Ser Phe Gly Ile Ser Gly Thr Asn Ala His Val Ile Leu Glu Gln
 2195 2200 2205
 Ala Ser Lys Thr Pro Asp Glu Thr Ala Asp Lys Ser Gly Pro Asp Ser
 2210 2215 2220
 Glu Ser Thr Val Asp Leu Pro Ala Val Pro Leu Ile Val Ser Gly Arg
 225 2230 2235 2240
 Thr Pro Ala Ala Leu Ser Ala Gln Ala Ser Ala Leu Leu Ser Tyr Leu
 2245 2250 2255
 Gly Glu Arg Gly Asp Ile Ser Thr Leu Asp Ala Ala Phe Ser Leu Ala
 2260 2265 2270
 Ser Ser Arg Ala Ala Leu Glu Glu Arg Ala Val Val Leu Gly Ala Asp
 2275 2280 2285
 Arg Glu Thr Leu Leu Ser Gly Leu Glu Ala Leu Ala Ser Gly Arg Glu
 2290 2295 2300
 Ala Ser Gly Val Val Ser Gly Ser Pro Val Ser Gly Gly Val Gly Phe
 305 2310 2315 2320
 Val Phe Ala Gly Gln Gly Gly Gln Trp Leu Gly Met Gly Arg Gly Leu
 2325 2330 2335

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Tyr Ser Val Phe Pro Val Phe Ala Asp Ala Phe Asp Glu Ala Cys Ala
 2340 2345 2350
 Gly Leu Asp Ala His Leu Gly Gln Asp Val Gly Val Arg Asp Val Val
 2355 2360 2365
 Phe Gly Ser Asp Gly Ser Leu Leu Asp Arg Thr Leu Trp Ala Gln Ser
 2370 2375 2380
 Gly Leu Phe Ala Leu Gln Val Gly Leu Leu Ser Leu Leu Gly Ser Trp
 385 2390 2395 2400
 Gly Val Arg Pro Gly Val Val Leu Gly His Ser Val Gly Glu Phe Ala
 2405 2410 2415
 Ala Ala Val Ala Ala Gly Val Leu Ser Leu Pro Asp Ala Ala Arg Met
 2420 2425 2430
 Val Ala Gly Arg Ala Arg Leu Met Gln Ala Leu Pro Ser Gly Gly Ala
 2435 2440 2445
 Met Leu Ala Val Ala Ala Gly Glu Glu Gln Leu Arg Pro Leu Leu Ala
 2450 2455 2460
 Asp Arg Val Asp Gly Ala Gly Ile Ala Ala Val Asn Ala Pro Glu Ser
 465 2470 2475 2480
 Val Val Leu Ser Gly Asp Arg Glu Val Leu Asp Asp Ile Ala Gly Ala
 2485 2490 2495
 Leu Asp Gly Gln Gly Ile Arg Trp Arg Arg Leu Arg Val Ser His Ala
 2500 2505 2510
 Phe His Ser Tyr Arg Met Asp Pro Met Leu Gln Glu Phe Ala Glu Ile
 2515 2520 2525
 Ala Arg Ser Val Asp Tyr Arg Arg Gly Asp Leu Pro Val Val Ser Thr
 2530 2535 2540
 Leu Thr Gly Glu Leu Asp Thr Ala Gly Val Met Ala Thr Pro Glu Tyr
 545 2550 2555 2560
 Trp Val Arg Gln Val Arg Glu Pro Val Arg Phe Ala Asp Gly Val Arg
 2565 2570 2575
 Val Leu Ala Gln Gln Gly Val Ala Thr Ile Phe Glu Leu Gly Pro Asp
 2580 2585 2590

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Ala Thr Leu Ser Ala Leu Ile Pro Asp Cys His Ser Trp Ala Asp Gln
2595 2600 2605

Ala Met Pro Ile Pro Met Leu Arg Lys Asp Arg Thr Glu Thr Glu Thr
2610 2615 2620

Val Val Ala Ala Val Ala Arg Ala His Thr Arg Gly Val Pro Val Glu
625 2630 2635 2640

Trp Ser Ala Tyr Phe Ala Gly Thr Gly Ala Arg Arg Val Glu Leu Pro
2645 2650 2655

Thr Tyr Ala Phe Gln Arg Gln Arg Tyr Trp Leu Glu Thr Ser Asp Tyr
2660 2665 2670

Gly Asp Val Thr Gly Ile Gly Leu Ala Ala Ala Glu His Pro Leu Leu
2675 2680 2685

Gly Ala Val Val Ala Leu Ala Asp Gly Asp Gly Met Val Leu Thr Gly
2690 2695 2700

Arg Leu Ser Val Gly Thr His Pro Trp Leu Ala Gln His Arg Val Leu
705 2710 2715 2720

Gly Glu Val Val Val Pro Gly Thr Ala Ile Leu Glu Met Ala Leu His
2725 2730 2735

Ala Gly Ala Arg Leu Gly Cys Asp Arg Val Glu Glu Leu Thr Leu Glu
2740 2745 2750

Thr Pro Leu Val Val Pro Glu Arg Ala Ala Gly Ala Gly Ser Arg Gly
2755 2760 2765

Pro Ala Gly Gly Thr Thr Val Ser Ile Glu Thr Ala Glu Glu Arg Val
2770 2775 2780

Arg Thr Asn Asp Ala Ile Glu Ile Gln Leu Leu Val Asn Ala Pro Asp
785 2790 2795 2800

Glu Gly Gly Arg Arg Arg Val Ser Leu Tyr Ser Arg Pro Ala Gly Gly
2805 2810 2815

Ser Arg Gly Gly Gly Trp Thr Arg His Ala Thr Gly Glu Leu Val Val
2820 2825 2830

Gly Thr Thr Gly Gly Arg Ala Val Pro Asp Trp Ser Ala Glu Gly Ala
2835 2840 2845

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Glu Ser Ile Ala Leu Asp Glu Phe Tyr Val Ala Leu Ala Gly Asn Gly
 2850 2855 2860

Phe Glu Tyr Gly Pro Leu Phe Gln Gly Leu Gln Ala Ala Trp Arg Arg
 865 2870 2875 2880

Gly Asp Glu Val Leu Ala Glu Ile Ala Pro Pro Ala Glu Ala Asp Ala
 2885 2890 2895

Met Ala Ser Gly Tyr Leu Leu Asp Pro Ala Leu Leu Asp Ala Ala Leu
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Gln Ala Ser Ala Leu Gly Asp Arg Pro Glu Gln Gly Gly Ala Trp Leu
 2915 2920 2925

Pro Phe Ser Phe Thr Gly Val Glu Leu Ser Ala Pro Ala Gly Thr Ile
 2930 2935 2940

Ser Arg Val Arg Leu Glu Thr Arg Arg Pro Asp Ala Ile Ser Val Ala
 945 2950 2955 2960

Val Met Asp Glu Ser Gly Arg Leu Leu Ala Ser Ile Asp Ser Leu Arg
 2965 2970 2975

Leu Arg Ser Val Ser Ser Gly Gln Leu Ala Asn Arg Asp Ala Val Arg
 2980 2985 2990

Asp Ala Leu Phe Glu Val Thr Trp Glu Pro Val Ala Thr Gln Ser Thr
 2995 3000 3005

Glu Pro Gly Arg Trp Ala Leu Leu Gly Asp Thr Ala Cys Gly Lys Asp
 3010 3015 3020

Asp Leu Ile Lys Leu Ala Thr Asp Ser Ala Asp Arg Cys Ala Asp Leu
 025 3030 3035 3040

Ala Ala Leu Ala Glu Lys Leu Asp Ser Ser Ala Leu Val Pro Asp Val
 3045 3050 3055

Val Val Tyr Cys Ala Gly Glu Gln Ala Asp Pro Gly Thr Gly Ala Ala
 3060 3065 3070

Ala Leu Ala Glu Thr Gln Gln Thr Leu Ala Leu Leu Gln Ala Trp Leu
 3075 3080 3085

Ala Glu Pro Arg Leu Ala Glu Ala Arg Leu Val Val Val Thr Cys Ala
 3090 3095 3100

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Ala Val Thr Thr Ala Pro Ser Asp Gly Ala Ser Glu Leu Ala His Ala
105 3110 3115 3120

Pro Leu Trp Gly Leu Leu Arg Ala Ala Gln Val Glu Asn Pro Gly Gln
3125 3130 3135

Phe Val Leu Ala Asp Val Asp Gly Thr Ala Glu Ser Trp Arg Ala Leu
3140 3145 3150

Pro Ser Ala Leu Gly Ser Met Glu Pro Gln Leu Ala Leu Arg Lys Gly
3155 3160 3165

Ala Val Arg Ala Pro Arg Leu Ala Ser Val Ala Gly Gln Ile Asp Val
3170 3175 3180

Pro Ala Val Val Ala Asp Pro Asp Arg Thr Val Leu Ile Ser Gly Gly
185 3190 3195 3200

Thr Gly Leu Leu Gly Gly Ala Val Ala Arg His Leu Val Thr Glu Arg
3205 3210 3215

Gly Val Arg Arg Leu Val Leu Thr Gly Arg Arg Gly Trp Asp Ala Pro
3220 3225 3230

Gly Ile Thr Glu Leu Val Gly Glu Leu Asn Gly Leu Gly Ala Val Val
3235 3240 3245

Asp Val Val Ala Cys Asp Val Ala Asp Arg Ala Asp Leu Glu Ser Leu
3250 3255 3260

Leu Ala Ala Val Pro Ala Glu Phe Pro Leu Cys Gly Val Val His Ala
265 3270 3275 3280

Ala Gly Ala Leu Ala Asp Gly Val Ile Glu Ser Leu Ser Pro Asp Asp
3285 3290 3295

Val Gly Ala Val Phe Gly Pro Lys Ala Ala Gly Ala Trp Asn Leu His
3300 3305 3310

Glu Leu Thr Arg Asp Thr Asp Leu Ser Phe Phe Ala Leu Phe Ser Ser
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Leu Ser Gly Val Ala Gly Ala Pro Gly Gln Gly Asn Tyr Ala Ala Ala
3330 3335 3340

Asn Ala Phe Leu Asp Ala Leu Ala His Tyr Arg Arg Ser Gln Gly Leu
345 3350 3355 3360

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 Thr Glu Thr Leu Ser Glu Val Asp Arg Ser Arg Ile Ala Arg Ala Asn
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 Pro Pro Leu Ser Thr Lys Glu Gly Leu Arg Leu Phe Asp Ala Gly Leu
 3395 3400 3405
 Ala Leu Asp Arg Ala Ala Val Val Pro Ala Lys Leu Asp Arg Thr Phe
 3410 3415 3420
 Leu Ala Glu Gln Ala Arg Ser Gly Ser Leu Pro Ala Leu Leu Thr Ala
 425 3430 3435 3440
 Leu Val Pro Pro Ile Arg Arg Asn Arg Arg Ala Ser Gly Thr Glu Leu
 3445 3450 3455
 Ala Asp Glu Gly Thr Leu Leu Gly Val Val Arg Glu His Ala Ala Ala
 3460 3465 3470
 Val Leu Gly Tyr Ser Ser Ala Ala Asp Val Gly Val Glu Arg Ala Phe
 3475 3480 3485
 Arg Asp Leu Gly Phe Asp Ser Leu Ser Gly Val Glu Leu Arg Asn Arg
 3490 3495 3500
 Leu Ala Gly Val Leu Gly Val Arg Leu Pro Ala Thr Ala Val Phe Asp
 505 3510 3515 3520
 Tyr Pro Thr Pro Arg Ala Leu Ala Arg Phe Leu His Gln Glu Leu Ala
 3525 3530 3535
 Asp Glu Ile Ala Thr Thr Pro Ala Pro Val Thr Thr Thr Arg Ala Pro
 3540 3545 3550
 Val Ala Glu Asp Asp Leu Val Ala Ile Val Gly Met Gly Cys Arg Phe
 3555 3560 3565
 Pro Gly Gln Val Ser Ser Pro Glu Glu Leu Trp Arg Leu Val Ala Gly
 3570 3575 3580
 Gly Val Asp Ala Val Ala Asp Phe Pro Ala Asp Arg Gly Trp Asp Leu
 585 3590 3595 3600
 Ala Gly Leu Phe Asp Pro Asp Pro Glu Arg Ala Gly Lys Thr Tyr Val
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Arg Glu Gly Ala Phe Leu Thr Asp Ala Asp Arg Phe Asp Ala Gly Phe
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Phe Gly Ile Ser Pro Arg Glu Ala Leu Ala Met Asp Pro Gln Gln Arg
 3635 3640 3645

Leu Leu Leu Glu Leu Ser Trp Glu Ala Ile Glu Arg Ala Gly Ile Asp
 3650 3655 3660

Pro Gly Ser Leu Arg Gly Ser Arg Thr Gly Val Phe Ala Gly Leu Met
 665 3670 3675 3680

Tyr His Asp Tyr Gly Ala Arg Phe Ala Ser Arg Ala Pro Glu Gly Phe
 3685 3690 3695

Glu Gly Tyr Leu Gly Asn Gly Ser Ala Gly Ser Val Ala Ser Gly Arg
 3700 3705 3710

Ile Ala Tyr Ser Phe Gly Phe Glu Gly Pro Ala Val Thr Val Asp Thr
 3715 3720 3725

Ala Cys Ser Ser Ser Leu Val Ala Leu His Leu Ala Gly Gln Ser Leu
 3730 3735 3740

Arg Ser Gly Glu Cys Asp Leu Ala Leu Ala Gly Gly Val Thr Val Met
 745 3750 3755 3760

Ser Thr Pro Gly Thr Phe Val Glu Phe Ser Arg Gln Arg Gly Leu Ala
 3765 3770 3775

Pro Asp Gly Arg Cys Lys Ser Phe Ala Glu Ser Ala Asp Gly Thr Gly
 3780 3785 3790

Trp Gly Glu Gly Ala Gly Leu Val Leu Leu Glu Arg Leu Ser Asp Ala
 3795 3800 3805

Arg Arg Asn Gly His Arg Val Leu Ala Val Val Arg Gly Ser Ala Val
 3810 3815 3820

Asn Gln Asp Gly Ala Ser Asn Gly Leu Thr Ala Pro Asn Gly Pro Ser
 825 3830 3835 3840

Gln Gln Arg Val Ile Gln Gln Ala Leu Ala Ser Ala Gly Leu Ser Val
 3845 3850 3855

Ser Asp Val Asp Ala Val Glu Ala His Gly Thr Gly Thr Arg Leu Gly
 3860 3865 3870

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Asp Pro Ile Glu Ala Gln Ala Leu Ile Ala Thr Tyr Gly Arg Asp Arg
 3875 3880 3885

Asp Pro Gly Arg Pro Leu Trp Leu Gly Ser Val Lys Ser Asn Ile Gly
 3890 3895 3900

His Thr Gln Ala Ala Ala Gly Val Ala Gly Val Ile Lys Met Val Met
 905 3910 3915 3920

Ala Met Arg His Gly Gln Leu Pro Arg Thr Leu His Val Asp Ala Pro
 3925 3930 3935

Ser Ser Gln Val Asp Trp Ser Ala Gly Arg Val Gln Leu Leu Thr Glu
 3940 3945 3950

Asn Thr Pro Trp Pro Asp Ser Gly Arg Pro Cys Arg Val Gly Val Ser
 3955 3960 3965

Ser Phe Gly Ile Ser Gly Thr Asn Ala His Val Ile Leu Glu Gln Ser
 3970 3975 3980

Thr Gly Gln Met Asp Gln Ala Ala Glu Pro Asp Ser Ser Pro Val Leu
 985 3990 3995 4000

Asp Val Pro Val Val Pro Trp Val Val Ser Gly Lys Thr Pro Glu Ala
 4005 4010 4015

Leu Ser Ala Gln Ala Ala Thr Leu Ala Thr Tyr Leu Asp Gln Asn Val
 4020 4025 4030

Asp Val Ser Pro Leu Asp Val Gly Ile Ser Leu Ala Val Thr Arg Ser
 4035 4040 4045

Ala Leu Asp Glu Arg Ala Val Val Leu Gly Ser Asp Arg Asp Thr Leu
 4050 4055 4060

Leu Ser Gly Leu Asn Ala Leu Ala Ala Gly His Glu Ala Ala Gly Val
 065 4070 4075 4080

Val Thr Gly Pro Val Gly Ile Gly Gly Arg Thr Gly Phe Val Phe Ala
 4085 4090 4095

Gly Gln Gly Gly Gln Trp Leu Gly Met Gly Arg Arg Leu Tyr Ser Glu
 4100 4105 4110

Phe Pro Ala Phe Ala Gly Ala Phe Asp Glu Ala Cys Ala Glu Leu Asp
 4115 4120 4125

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Asp Glu Ser Leu Leu Asp Arg Thr Leu Trp Ala Gln Ser Gly Leu Phe
 145 4150 4155 4160

Ala Leu Gln Val Gly Leu Trp Glu Leu Leu Gly Thr Trp Gly Val Arg
 4165 4170 4175

Pro Ser Val Val Leu Gly His Ser Val Gly Glu Leu Ala Ala Ala Phe
 4180 4185 4190

Ala Ala Gly Val Leu Ser Met Ala Glu Ala Ala Arg Leu Val Ala Gly
 4195 4200 4205

Arg Ala Arg Leu Met Gln Ala Leu Pro Ser Gly Gly Ala Met Leu Ala
 4210 4215 4220

Val Ser Ala Thr Glu Ala Arg Val Gly Pro Leu Leu Asp Gly Val Arg
 225 4230 4235 4240

Asp Arg Val Gly Val Ala Ala Val Asn Ala Pro Gly Ser Val Val Leu
 4245 4250 4255

Ser Gly Asp Arg Asp Val Leu Asp Gly Ile Ala Gly Arg Leu Asp Gly
 4260 4265 4270

Gln Gly Ile Arg Ser Arg Trp Leu Arg Val Ser His Ala Phe His Ser
 4275 4280 4285

His Arg Met Asp Pro Met Leu Ala Glu Phe Ala Glu Leu Ala Arg Ser
 4290 4295 4300

Val Asp Tyr Arg Ser Pro Arg Leu Pro Ile Val Ser Thr Leu Thr Gly
 305 4310 4315 4320

Asn Leu Asp Asp Val Gly Val Met Ala Thr Pro Glu Tyr Trp Val Arg
 4325 4330 4335

Gln Val Arg Glu Pro Val Arg Phe Ala Asp Gly Val Gln Ala Leu Val
 4340 4345 4350

Asp Gln Gly Val Asp Thr Ile Val Glu Leu Gly Pro Asp Gly Ala Leu
 4355 4360 4365

Ser Ser Leu Val Gln Glu Cys Val Ala Glu Ser Gly Arg Ala Thr Gly
 4370 4375 4380

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Ile Pro Leu Val Arg Arg Asp Arg Asp Glu Val Arg Thr Val Leu Asp
 385 4390 4395 4400

Ala Leu Ala Gln Thr His Thr Arg Gly Gly Ala Val Asp Trp Gly Ser
 4405 4410 4415

Phe Phe Ala Gly Thr Arg Ala Thr Gln Val Asp Leu Pro Thr Tyr Ala
 4420 4425 4430

Phe Gln Arg Gln Arg Tyr Trp Leu Glu Pro Ser Asp Ser Gly Asp Val
 4435 4440 4445

Thr Gly Val Gly Leu Thr Gly Ala Glu His Pro Leu Leu Gly Ala Val
 4450 4455 4460

Val Pro Val Ala Gly Gly Asp Glu Val Leu Leu Thr Gly Arg Leu Ser
 465 4470 4475 4480

Val Gly Thr His Pro Trp Leu Ala Glu His Arg Val Leu Gly Glu Val
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Val Val Pro Gly Thr Ala Leu Leu Glu Met Ala Trp Arg Ala Gly Ser
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Gln Val Gly Cys Glu Arg Val Glu Glu Leu Thr Leu Glu Ala Pro Leu
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Val Leu Pro Glu Arg Gly Ala Ala Ala Val Gln Leu Ala Val Gly Ala
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Pro Asp Glu Ala Gly Arg Arg Ser Leu Gln Leu Tyr Ser Arg Gly Ala
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Asp Glu Asp Gly Asp Trp Arg Arg Ile Ala Ser Gly Leu Leu Ala Gln
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Ala Gly Gln Val Asp Leu Ala Glu Phe Tyr Glu Arg Leu Ala Glu Arg
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Gly Leu Thr Tyr Gly Pro Val Phe Gln Gly Leu Arg Ala Ala Trp Arg
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His Gly Asp Asp Ile Phe Ala Glu Leu Ala Gly Ser Pro Asp Ala Ser
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Gly Phe Gly Ile His Pro Ala Leu Leu Asp Ala Ala Leu His Ala Met
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 Ala Leu Gly Ala Ser Pro Asp Ser Glu Ala Arg Leu Pro Phe Ser Trp
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 4675 4680 4685
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 Ser Thr Asp Gln Ile Gly Ala Gly Arg Gly Asp Gln Glu Arg Leu Leu
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 4995 5000 5005

Pro Ala Glu Asn Pro Leu Arg Val Val Val His Ala Ala Gly Val Leu
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<211> 2363

<212> DNA

<213> *Saccharopolyspora spinosa*

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2363

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<211> 990

<212> DNA

<213> *Saccharopolyspora spinosa*

<220>

<221> CDS

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<223> ORF23; dNTP-Glucose-4,6-Dehydratase

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Val Arg Gln Leu Leu Gly Gly Ala Tyr Pro Ala Phe Ala Asp Ala Asp	
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Val Val Val Leu Asp Lys Leu Thr Tyr Ala Gly Asn Glu Ala Asn Leu	
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Ala Pro Val Ala Asp Asn Pro Arg Leu Lys Phe Val Cys Gly Asp Ile	
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Cys Asp Arg Glu Leu Val Gly Gly Leu Met Ser Gly Val Asp Val Val	
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Val His Phe Ala Ala Glu Thr His Val Asp Arg Ser Ile Thr Gly Ser	
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gac gcc ttc gtg atc acc aac gtg gtc ggc acc aac gtg ctg ctg cag	336
Asp Ala Phe Val Ile Thr Asn Val Val Gly Thr Asn Val Leu Leu Gln	
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Ala Ala Leu Asp Ala Glu Ile Gly Lys Phe Val His Val Ser Thr Asp	
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Glu Val Tyr Gly Ser Ile Glu Asp Gly Ser Trp Pro Glu Asp His Ala	
130 135 140	
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Leu Glu Pro Asn Ser Pro Tyr Ser Ala Ala Lys Ala Gly Ser Asp Leu	
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Leu Ala Arg Ala Tyr His Arg Thr His Gly Leu Pro Val Cys Ile Thr	
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Arg Cys Ser Asn Asn Tyr Gly Pro Tyr Gln Phe Pro Glu Lys Val Leu	

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Gly Asp Gly Leu Asn Val Arg Asp Trp Leu His Val Ser Asp His Cys			
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Arg Gly Ile Gln Leu Val Ala Asp Ser Gly Arg Ala Gly Glu Ile Tyr			
225	230	235	240
aac atc ggc ggc ggc acc gag ctg acc aac aac gag ctg acc gag cgg			768
Asn Ile Gly Gly Gly Thr Glu Leu Thr Asn Asn Glu Leu Thr Glu Arg			
245	250	255	
ctg ctg gca gag ctg ggc ctc gac tgg tcg gtg gtg cgg ccg gtc acc			816
Leu Leu Ala Glu Leu Gly Leu Asp Trp Ser Val Val Arg Pro Val Thr			
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Asp Arg Lys Gly His Asp Arg Arg Tyr Ser Val Asp His Ser Lys Ile			
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Val Glu Glu Leu Gly Tyr Ala Pro Gln Val Asp Phe Glu Thr Gly Leu			
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cgc gag aca atc cgc tgg tac cag gac aac cgg gac tgg tgg gag ccg			960
Arg Glu Thr Ile Arg Trp Tyr Gln Asp Asn Arg Asp Trp Trp Glu Pro			
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<210> 53

<211> 329

<212> PRT

<213> Saccharopolyspora spinosa

<400> 53

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Cys Asp Arg Glu Leu Val Gly Gly Leu Met Ser Gly Val Asp Val Val
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Asp Ala Phe Val Ile Thr Asn Val Val Gly Thr Asn Val Leu Leu Gln
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Glu Val Tyr Gly Ser Ile Glu Asp Gly Ser Trp Pro Glu Asp His Ala
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Leu Glu Pro Asn Ser Pro Tyr Ser Ala Ala Lys Ala Gly Ser Asp Leu
 145 150 155 160

Leu Ala Arg Ala Tyr His Arg Thr His Gly Leu Pro Val Cys Ile Thr
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Arg Cys Ser Asn Asn Tyr Gly Pro Tyr Gln Phe Pro Glu Lys Val Leu
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Pro Leu Phe Ile Thr Asn Leu Met Asp Gly Ser Gln Val Pro Leu Tyr
 195 200 205

Gly Asp Gly Leu Asn Val Arg Asp Trp Leu His Val Ser Asp His Cys
 210 215 220

Arg Gly Ile Gln Leu Val Ala Asp Ser Gly Arg Ala Gly Glu Ile Tyr
 225 230 235 240

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<210> 54

<211> 918

<212> DNA

<213> Saccharopolyspora spinosa

<220>

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 Ser Glu Leu Ala Arg Ile Leu Pro Ala Arg Thr Gly Ala Leu Val His
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 Arg Pro Gly Ser Gly Glu Leu Asp Val Thr Asp Ala Glu Glu Val Ala
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gac gcg ttg ggt tcc ttc gcg gag acg gcg aag gac gcg gag ctg cga 192
 Asp Ala Leu Gly Ser Phe Ala Glu Thr Ala Lys Asp Ala Glu Leu Arg
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 Pro Val Val Ile Asn Ala Ala Ala Tyr Thr Ala Val Asp Ala Ala Glu
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 Thr Asp Tyr Val Phe Pro Gly Asp Gly Ala Arg Pro Tyr Glu Pro Thr
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 Arg Leu Ser Gly Glu Arg Asp Thr Leu Ser Val Val Asp Asp Gln Ile
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 Gly Ser Pro Thr Trp Ala Ala Asp Leu Ala Ser Gly Leu Leu Glu Leu
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 Cys Thr Asn Ser Gly Gln Val Thr Trp Tyr Glu Phe Ala Arg Ala Ile
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 Arg
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<210> 55

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<212> PRT

<213> Saccharopolyspora spinosa

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Asp Ala Leu Gly Ser Phe Ala Glu Thr Ala Lys Asp Ala Glu Leu Arg
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Pro Val Val Ile Asn Ala Ala Ala Tyr Thr Ala Val Asp Ala Ala Glu
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Leu Ala Lys Ala Cys Arg Ser Ser Gly Leu Pro Leu Val His Val Ser
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Thr Asp Tyr Val Phe Pro Gly Asp Gly Ala Arg Pro Tyr Glu Pro Thr
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245 250 255

Ala Asp Phe Pro Leu Pro Ala His Arg Pro Ala Tyr Ser Val Leu Ser
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275 280 285

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Arg
305

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